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g) Alkyl(meth)acrylat-Polymeren und -Copolymeren mit einem zahlenmittleren Molekulargewicht von etwa 100 000 bis 1 000 000, insbesondere Ethylacrylat/Methylmethacrylat-Copolymeren und Methylacrylat/Ethylacrylat-Copolymeren;

h) Polyvinylacetat mit einem zahlenmittleren Molekulargewicht von etwa 250 000 bis 700 000, ggf. stabilisiert mit Polyvinylpyrrolidon.

10 12. Futtermittelzusatz nach Anspruch 11, gekennzeichnet durch eine mittlere Korngröße von etwa 0,4 bis 2 mm aufweisen.

13. Futtermittelzusatz nach Anspruch 11 oder 12, dadurch gekennzeichnet, dass er wenigstens ein Enzym enthält, das ausgewählt ist unter Oxidoreduktasen, Transferasen, Lyasen, Isomerasen, Ligasen, Phosphatasen und Hydrolasen.

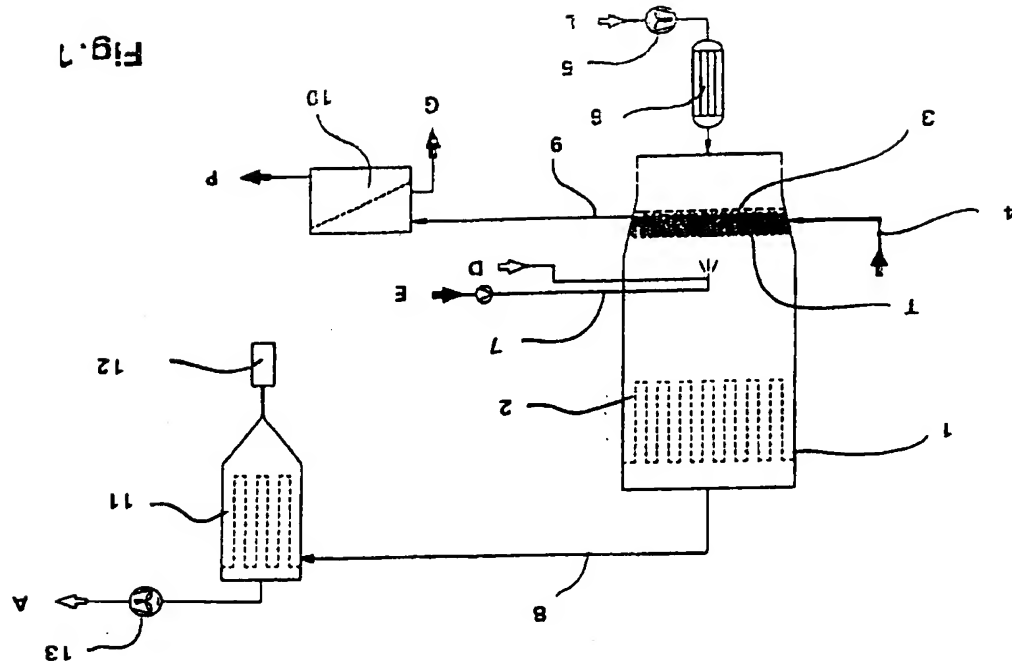
14. Futtermittelzusatz nach Anspruch 13, dadurch gekennzeichnet, dass die Hydrolase ein Nichtstärkopolysaccharid-spaltendes Enzym ist.

15. Futtermittelzusatz nach Anspruch 14, dadurch gekennzeichnet, dass die Phosphatase Phytase ist.

25 16. Futtermittelzusatz nach Anspruch 15, dadurch gekennzeichnet, dass er $1 \cdot 10^3$ bis $1 \cdot 10^5$ U Phytase pro Gramm Gesamtgewicht umfasst.

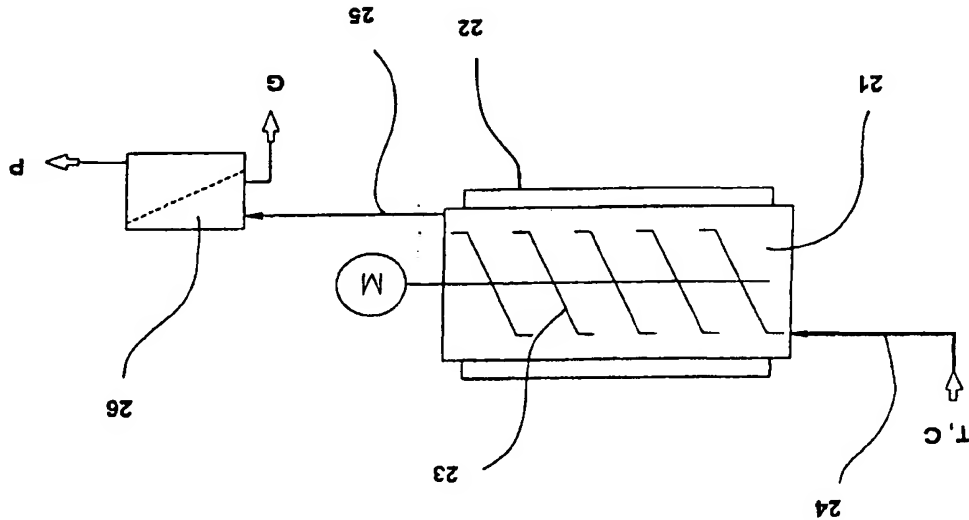
17. Pelletierte Futtermittelzusammensetzung, welche neben Übli-
30 chen Bestandteilen wenigstens einen Futtermittelzusatz nach
einem der Ansprüche 11 bis 16 als Beimischung enthält.

18. Verwendung eines Futtermittelzusatzes nach einem der Ansprüche 11 bis 16 zur Herstellung von pelletierten Futtermittelzusammensetzungen.



2/2

Fig. 2



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INTERNATIONAL SEARCH REPORT

IPC Class. No.		PCT/EP 00/05793	
A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A23K1/00 A23K1/165			
According to International Patent Classification (IPC) or to both national classification and IPC			
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A23K			
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched			
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, MPI Data, PAJ, CHEM ABS Data, CAB Data			
C. DOCUMENTS CONSIDERED TO BE RELEVANT			
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	
E	WO 00 47060 A (DSM NV; ANDELA CARL STONITUS MARIA (NL); KLEIN HOLKENBORG AUGUSTIN) 17 August 2000 (2000-08-17) examples 4-8 claims 1-4, 12-25	1-7, 11-18	
E	WO 00 36927 A (BASF AG; BETZ ROLAND (DE); HARZ HANS PETER (DE); HEINZL WOLFGANG ()) 29 June 2000 (2000-06-29) page 2, line 38 - line 47 page 3, line 8 - line 15 page 3, line 33 - line 36 page 4, line 1 - line 6 page 4, line 40 - page 5, line 27 page 6, line 1 - page 7, line 32 claims 1-8	1, 10-18	
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.			
* Special categories of cited documents: "A": document defining the general state of the art which is not considered to be of particular relevance "E": earlier document but published on or after the international filing date "L": document which may throw doubt on priority (claims) or which is cited to establish the publication date of another document or other special reason (as specified) "O": document referred to in oral disclosure, use, exhibition or other means "P": document published prior to the international filing date but later than the priority date (claim) "T": later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X": document of particular relevance the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y": document of particular relevance the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents "Z": document of particular relevance the claimed invention is not considered to be obvious to a person skilled in the art "S": document member of the same patent family			
Date of the actual completion of the international search:		Date of mailing of the international search report	
15 November 2000		24/11/2000	
Name and mailing address of the ISA European Patent Office, P.O. Box 5018 Patentamt 2 74 500 Nußlingen Tel. (+31-70) 340-2040, Tlx. 31 651 epo nl Fax: (+31-70) 340-3016		Authorized officer: Dekretel, H	

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C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		Int. Journal Application No. PCT/EP 00/05793
Category *	Citation or document, with indication where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 97 12958 A (GENENCOR INT) 10 April 1997 (1997-04-10) page 3, last paragraph - page 4, paragraph 1 page 5, paragraph 3 - paragraph 4 examples 1-10 Claims 1-7	1, 2, 4-6, 11-13
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Form PCT/ISA/210 (Continuation of standard form) (July 1992)

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			US 6083538 A
			27-04-1999
			04-07-2000

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Mit. Anzahl Mitteilungen				PCT/EP 00/05793	
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		US 6083538 A	04-07-2000		



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(21) International Application Number: PCT/US98/26628 (22) International Filing Date: 15 December 1998 (15.12.98)	(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CT, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).
(30) Priority Data: 60069591 60095283 15 December 1997 (15.12.97) US 4 August 1998 (04.08.98) US (71)(72) Applicant and Inventor: RON, Eyal, S. (US/US); 7 Coach Road, Lexington, MA 02420 (US).	Published Without international search report and to be republished upon receipt of that report.
(54) Title: ASPECTED PARTICLES FOR ORAL DELIVERY (57) Abstract Aa oral delivery vehicle includes an aspected particle including a pharmaceutically active component and excipients, wherein the vehicle is formulated and/or constructed and arranged to provide controlled delivery of the pharmaceutically active component. The aspected particle possesses one dimension that is about an order of magnitude smaller than the other two dimensions. The vehicle may further contain a tuberculous coating to improve mouth-feel. The vehicle may further contain a coating to provide sustained drug delivery to the particle.	

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ASPECTED PARTICLES FOR ORAL DELIVERY

This application claims priority under 37 C.F.R. §119(c) to co-pending application U.S.S.N. 60/069,501 filed December 15, 1997, "Oral Delivery Formulations", and to co-pending application U.S.S.N. 60/095,283 filed August 4, 1998, entitled "Aspected Microparticles for Oral Delivery", the contents of which are incorporated herein in their entirety.

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Field of Invention

This invention relates to controlled-release pharmaceutical compositions in a aspected geometry dosage form for the administration of drugs.

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Background of the Invention

Current orally delivered drugs are formulated in either solid (i.e., tablet, capsule or granules) or liquid (i.e., solution, suspension or emulsion) form. Solid dosage forms are conventionally the dosage forms of choice as they are typically more stable, less expensive to manufacture and have achieved general acceptance by consumers. The manufacture of solid dosage forms typically involves the processing of the drug with suitable excipients in order to produce a freely flowing powder. The type of processing and excipients chosen to manufacture the powder can be altered to provide desired effects such as controlled release of the drug. Once processed, the powder can be directly packaged into sachets, compressed into tablets or filled into capsules. Tablets can further be coated in order to improve palatability or provide controlled release of the drug.

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The pediatric population and those who experience difficulty in swallowing primarily use liquid dosage forms. Liquid dosage forms are available orally as solutions, suspensions or emulsions. These liquids often contain colorants and flavorings in an attempt to increase palatability and patient acceptance.

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Over 35% of the population are unable to adequately ingest either solid or liquid dosage forms due to physical limitations that include difficulty in swallowing due to esophageal dehydration, "mouth breathing", esophageal lesions or consumption

of anticholinergic medications. Geriatric patients also experience difficulty in chewing due to reduced bulk and tone of oral musculature as well as loss of or degradation in the quality of teeth.

In order to overcome this inability to tolerate solid dosage forms, health care providers typically crush solid dosage forms and disperse them in a semi-solid medium (e.g., applesauce, pudding, etc.). However, when tablets or capsules are tampered with the drug release kinetics of the pharmaceuticals are altered. This results in dosing times and concentrations that are sub-optimal. Therefore, pharmaceutical manufacturers provide many drugs with the instructions: "DO NOT CRUSH" (*Hospital Pharmacy*, 21(1), 27, 1996).

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Fast dissolving tablets are available as an alternative to pill dosage formats.

The tablets are retained in the mouth and rapidly dissolve to release the drug.

Limitations to this method include restriction to drugs which do not have unacceptably unpleasant or bitter taste and the immediate release of the drug which prevents sustained release.

15

A further factor in patient drug non-compliance is the aesthetic response of the patient to the dosage format. When the "mouth-feel" of the dose is unpleasant, the patient is less likely to comply with the dosage regimen. The term mouth-feel is related to the type of sensation or touch that a dosage form produces in the mouth upon ingestion and is not concerned with the chemical stimulation of olfactory nerves or taste buds. However for the formulation to be successful, the overall effect in the mouth is important. In general, gritty or gummy textures are undesirable. A smooth texture is preferred. See, *Pharmaceutical Dosage Forms*, Edited by Lieberman, H.A. and Lachman, L. Marcel Dekker, Inc. New York, Volume I, pp. 291.

Currently available are free flowing particulate drug platforms in the form of rounded spheres which are currently marked under the tradenames Spoon Dose™ (Fuisz) and Pharmazome™ (Elan). The powders are added directly to food or drinks by the user just prior to ingestion. While such a drug delivery mechanism may be attractive to those wishing to avoid pills, the particles still retains their sense of grittiness and provides an unacceptable mouth-feel to the user.

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In attempts to address some of the above issues, different formulations have been investigated. Formulations of nano- or macrogranulars have been reported in US

5,618,527. In order to prevent the sensation of grittiness US 5,618,527 describes formulations in either liquid or tablet form consisting of spherical particles of not greater than 125 μm in diameter. Additionally, the particles are required to have smooth edges. These requirements severely limit the flexibility of the drug delivery of the drug.

An alternative attempt to reduce the sensation of grittiness by using a blend of a gritty drug product with a seedy fruit, such as strawberries, was described in US 5,102,664. In this combination, the seedy fibrous fruit texture masks the grittiness of the drug.

Flake-like geometries have been used to improve patient compliance in the administration of dosage formats. Peters *et al.* in US 4,581,232 describes the use of a flake-like structure for the microencapsulation of drugs in order to produce a suitable taste-masking effect for bitter after-taste medications. While the flake-format reduced patient aversion to the medication, the flake format yielded rapid bioavailability. Thus, this formulation was an unstable format for controlled drug delivery.

There is a need for controlled-release formulations for pharmaceutical administrations that are easy to ingest; have a time-dependent release that offset the short half-life of the active ingredient and thus minimize multiple dosages; exhibit satisfactory stability; and are sufficiently palatable and convenient to administer and that possess the appropriate mouth feel to ensure patient compliance. These and other limitations of the prior art are met in the present invention.

Summary of the Invention

It is an object of the invention to provide an oral drug delivery platform that is easy to ingest and retain and that does not possess the limitations of prior art solid and liquid form dosages. It is a further object of the invention to provide a drug delivery format that is spoon feedable.

It is a further object of the present invention to provide an alternative drug dosage format to the pill or capsule format.

It is a further object of invention to provide a drug delivery vehicle with enhanced mouth feel for increased patient compliance. It is a further object of the invention to provide a drug delivery vehicle with an acceptable organoleptic-feel.

The term organoleptic-feel is related to the stimulating any of the organs of sensation (PDR Medical Dictionary, Medical Economics, Montvale, NJ, 1995).

It is still a further object of the invention to provide a dosage form that is easy to ingest, and that provides a reservoir for controlled delivery of the drug.

These and other objects of the invention are achieved by the drug delivery platforms of the invention.

The present invention provides an oral delivery platform which overcomes the noncompliance issues in the geriatric and other patient populations and which optimizes the absorption of drugs.

The present invention provides a sustained delivery vehicle. The vehicle includes a pharmaceutically active component and other pharmaceutical acceptable excipients. The vehicle is flat or of an aspected morphology which provides an acceptable mouth feel. By aspected morphology, as that term is used herein, it is meant that at least one dimension of the vehicle is considerably smaller than the scale of the largest dimension. The smallest dimension may be one order of magnitude smaller than the largest dimension and may be up to three orders of magnitude (1000-fold) smaller. The vehicle is formulated and/or constructed and arranged to provide controlled delivery of the pharmaceutically active component to the desired site within the patient.

The aspected particles may be administered to the patient as a free-flowing powder. Alternatively, the aspected particles may be incorporated into a viscous base having a consistency capable of being spoon-fed. The viscous base may be food or non-food, such as by way of example, applesauce or cellulosic gel. The aspected particles optionally may be provided premixed with the base or it may be supplied separately from the base for mixing just prior to consumption. A delivery vehicle comprised of aspected particles including a pharmaceutically active component may be added to or mixed into the viscous base. The vehicle is flat of an aspected morphology which provides an acceptable mouth feel, while the viscous base facilitates swallowing and masks the presence of the drug. The vehicle may be formulated and/or constructed and arranged to instant release or to provide controlled delivery of the pharmaceutically active component to the desired site within the patient.

Use of highly aspected particles as a drug delivery vehicle provides significant benefits in controlling the release kinetics of a drug. Aspected particles provide uniform surfaces for drug diffusion and release over time. In addition, aspected particles experience a much less dramatic change in volume/surface area ratio as the particles dissolve, as compared to spherical particles. Where the volume/surface area ratio remains relatively constant, drug delivery vehicle architecture and design is simplified. Highly aspected particles for use in drug delivery vehicles may incorporate features known to be effective in the controlled release of drugs. For example, the release kinetics of the drug may be controlled by incorporation of hydrophobic or water-insoluble excipients to the aspected particle in order to retard drug dissolution. Similarly, coating the aspected particle with hydrophobic or water-insoluble polymeric films provides controlled drug release. Incorporation of the appropriate excipients into the aspected drug delivery vehicle provides controlled release kinetics

In one embodiment of the invention, the particles are coated to enhance mouth-feel. The particles may be coated with a fast swellable hydrogel, which results in enhanced palatability and mouth feel upon wetting. In another embodiment of the invention, the drug-incorporated aspected particles may be coated with a suitable film-former polymer or hydrogel that eliminates the damage to the epithelial cells of the esophagus additionally to enhancing the mouth-feel.

In one aspect of the invention, the drug delivery vehicle is provided in a flat morphology. The drug-incorporated aspected particles may be administered in a variety of media, including liquid, tablet and food-feedable bases. The aspected particles are formulated to provide all the benefits for controlling the release kinetics of the drug as described herein.

An additional feature of the invention is that the flat morphology of the particles eliminates or reduces any unpleasant organoleptic sensations. The aspected particles are coated with a gel which forms a waterlike environment surrounding the particle. The mouth does not "see" the particle and no sensory reaction occurs.

The drug delivery vehicle and the spoon-feedable drug delivery vehicle described herein overcome the limitations of the prior art in providing a dosage format that is easy to administer, provides controlled drug release kinetics and

improves patient compliance. An further advantage of the present invention, includes increased ease of manufacturing and processing control. This alleviates of many of the shortcomings of nano- and macro-granules in terms of particle size and manufacturing constraints when dealing with spherical particles.

Brief Description of the Drawing

This invention is described with reference to the Figures, which are presented for the purpose of illustration only and which are in not limiting of the invention and in which:

Figure 1 is a schematic illustration of an aspected particle demonstrating the difference between flat particle dissolution and spherical particle in terms of constant surface/ volume ratio;

Figure 2 is a cross-sectional view of a hydrogel coated aspected particle that swells upon contact with water;

Figure 3 is a schematic illustration of multilayers aspected particles in which 3A illustrates drug layers in center layer "sandwiched" between two layers which do not contain drug but control the mouth-feel and the release rate; and 7B illustrates three different layers which may or may not contain drug.

Figure 4 is a cross-sectional view of an aspected particle having a core containing the pharmaceutically active agent and a film forming coating to control diffusion and release of the drug;

Figure 5 is a schematic illustration of a aspected particulates having a core of swellable hydrogel, drug and an outer membrane in which the swellable hydrogel core assists to push the drug from the aspected particle out in a controlled fashioned through the coating;

Detailed Description of the Invention

The present invention provides a novel oral drug delivery platform. The drug delivery vehicle may be advantageous in the administration of drugs to patients who experience difficulties in swallowing and/or tolerating medication in pills or tablets form. According to the invention, the drug may be incorporated into aspected particles that can be directly administered to the patient or that can be introduced

into foods, aqueous liquids or semi-solid bases to form a spoon-able or drinkable drug delivery system. The aspected particle may be readily administered to a patient to provide rapid or sustained drug delivery without leaving an undesirable organoleptic feel.

5 It has been observed previously that spherical or granular particulates leave an undesirable mouth-feel. The present invention has recognized that drugs that are incorporated into aspected particles possess enhanced mouth-feel by eliminating or reducing the gritty feel in the mouth. Because the flat morphology has a better mouth feel than current spherical delivery vehicles, e.g., U.S. 5,516,537, it is anticipated that they will be better tolerated by the patient, leading to more complete dosages and higher compliance.

The present invention also recognizes that oral dosage forms containing pharmaceutically active substances that are apportioned into many individual units, here the aspected particle of the invention, are more reliable in their biopharmaceutical behavior. Upon ingestion the particles spread over a large section of the incistinal tract and provide a improved uptake of the released drug. Also, the movement and quantity of the digestive fluids do not noticeably influence multiparticulate dosage forms, owing to the large number of individual particles that compensate for each other. Therefore, bioavailability is more reliable in such multiparticulate form than in monolithic dosage forms.

The aspected particle of the present invention, used as a drug delivery vehicle, includes pharmaceutical active or drug and a synthetic polymer or naturally occurring material which is compatible with the drug. The particle has an aspected pseudo-two dimensional morphology. By aspected morphology, as that term is used herein, it is meant that at least one dimension of the vehicle is considerably smaller than the scale of the largest dimension.

Figure 1 illustrates a highly aspected particle of the invention. An aspected particle 10 is formulated to include a desired pharmaceutical agent. It may further include a base and suitable excipients to provide desired properties, such as stability. The particle 10 is aspected, by which it is meant, that the particle has at least one dimension which is much smaller than the largest dimension of the particle. The smallest dimension may be one order of magnitude smaller than the largest

dimension and may be up to three orders of magnitude (1000-fold) smaller. The thickness of the aspected particle typically is the dimension which is smaller than the width or length. Typically the width to thickness ratio is in the range of 3:1 to about 1000:1. In preferred embodiments, the particle is about 100 nm to about 10 mm along the longest dimension.

The particle may be a substantially flat, thin layer, and thus possesses one dimension that is substantially less than the other two dimensions. The particle may be substantially planar or somewhat curvilinear. It may have an uneven surface, such as breakfast cereal flake. The particles are preferably free flowing and are of relatively uniform and consistent size and morphology.

The particle also includes pharmaceutically acceptable excipients to aid in the preparation of a stable pharmaceutical composition. Excipients include additives which have no therapeutic effect but which provide a desirable attribute to the drug delivery vehicle. Pharmaceutically acceptable excipients are well known and understood by those skilled in the art. Exemplary excipients include antioxidants, fillers, buffers, antibiotics, flavoring, colorants, adhesives, binders and the like. In particular, the pharmaceutically active compound may be incorporated into a natural or synthetic base or filler with which it is compatible. Suitable fillers include cellulose, poloxaners and polyethyleneglycols.

The aspected nature of the particle according to the invention provides a reduced organo-leptic sensation; however, the particles may be further modified to improve mouth-feel.

In one aspect of the invention, the aspected particle is coated with a lubricious layer. The lubricious layer is slippery to the touch which facilitates the swallowing of the particles. An additional advantage of the hydrogel-coated particle is that the low friction surface reduces damage to the epithelial cells of the esophagus in addition to enhancing mouth-feel. The lubricious coating may be a hydrophobic or hydrophilic coating. Materials suitable for hydrophobic coating includes oils, such as silicone oils or siloxanes, and other low friction materials.

Materials suitable for hydrophilic coatings include hydrogel polymer which become hydrated and swell in contact with an aqueous medium. The lubricious layer may contain flavorings and colorants for further enhancement of consumer appeal.

In preferred embodiments, the aspected particles of the invention are coated with an appropriate hydrogel. The hydrogel-coated particle swells upon contact with water to provide a smooth sensation and texture that enhances the mouth-feel and allows as easy as possible swallowing. Figure 2 demonstrates a hydrogel-coated, highly aspected particle 20 of the invention. A flat or aspected particle 10 is formulated, as in Figure 1, to include a desired pharmaceutical agent. The particle 10 may be coated with a gel coating 22. Upon exposure to moisture, for example, in the mouth or other body cavities, the coating swells to give a lubricious, slippery coating. Exemplary hydrogels include, by way of example only,

polyvinylpyrrolidone, polyvinyl alcohols, poly(N-vinyl lactams), polyethylene oxides, polyvinyl ethers, poly(acrylic acids) and derivatives thereof.

The aspected particles may be dispersed in an aqueous carrier substantially immediately prior to administration. The aspected particles are thereby combined with one or more gelling or swelling agents capable of forming a viscous medium around the particles in an aqueous carrier as well as being provided with a masking surface layer when dispersed in the aqueous carrier. This serves to mask uneven surfaces on the aspected particles and prevent them from adhering to oral mucosa when the composition is ingested and thus makes it easier to administer large dosages of an active substance. The masking surface layer is preferably provided by an increased viscosity of the viscous medium in the immediate vicinity of the particles relative to the viscosity of the surrounding aqueous carrier. A ready-to-use composition is prepared by mixing the composition with an aqueous carrier substantially immediately prior to administration of the composition.

In another aspect of the invention, the aspected particle of the invention is formulated to provide a desired kinetics of drug release. The particle may be designed for instantaneous release or for sustained release over periods of hours to days. The particle may be designed for linear (zero or first order), or non-linear drug release kinetics. The aspected morphology provides certain advantages over a spherical particle in drug release kinetics. The release kinetics from a spherically shaped delivery system is highly dependent on the surface area to volume ratio of the sphere. This ratio is highly dependent on the size distribution of the spheres. In contrast, with flat morphology the surface area to volume ratio is essentially

independent of the size. This is demonstrated in Figure 1, which shows the relatively constant surface area for an aspected particle 20 as it dissolves. Surface area changes as a function of the square of the particle dimensions in a pseudo-rectangular or disc-like particle, such as the aspected particle 20. This is compared to the dramatic change in surface area spherical particle 22, which is a cubic relationship. The surface area of a sphere changes as a cubic function of the radius. This in turn means more precisely controlled release kinetics. See, Ron and Langer (Chapter 4) and Gupta and Robinson (Chapter 6) in *Treatise on Controlled Drug Delivery Fundamentals, Optimization, Applications*; Edited by Agis Kydonieus, Marcel Dekker, Inc., New York, 1991; for additional information, which is hereby incorporated by reference.

Selection of the appropriate additives or excipients also effects controlled drug delivery. Additionally, the particle may contain inert excipients to control drug stability and dissolution rates. Incorporating hydrophobic and/or water insoluble polymers in the system will impede the rate of water penetration into the system and therefore will slow down the dissolution rate of the drug. Thus, the release rate is controlled, in part, by the relative solubilities of the drug and base excipients. For example, for a water soluble drug, one may choose a water-insoluble base to retard the release rate of the drug. Similarly, for a water-soluble drug one may select a water-insoluble base to retard delivery.

Exemplary excipients for this purpose include polyvinyl alcohol, polyvinylpyrrolidone, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, agar, carrageenan, xanthan, polyethylene glycol, a copolymer of acrylic and methacrylic acid esters, ethylcellulose, cellulose acetate, cellulose acetate phthalate, poly(methyl methacrylate), poly(methyl acrylate), polyethylene, polypropylene, poly(ethylene oxide), PET, poly(vinyl isobutyl ether), poly(vinyl acetate), poly(vinyl chloride), polyurethane, pectin, furcellaran, starch, zinc, gelatin, collagen, polygelins, alginate acid, propylene glycol alginate or sodium alginate. One embodiment of the invention utilizes a matrix layer of a water soluble or swellable polymers, such as hydroxypropyl cellulose (e.g., 40-95% by weight and having a molecular weight above 100,000) and a homopolymer of ethylene oxide (e.g., 5-60 wt% and having a molecular weight from 3,000,000 to 5,000,000), a

water-insoluble polymer selected from the group consisting of ethyl cellulose, propyl cellulose, polyethylene and polypropylene (0-10wt%) and 2-10% of a plasticizer for controlled drug delivery.

The use of specific polymeric and hydrogel coatings allows engineering of drug products capable of being delivered to a patient in a relatively targeted fashion. In one embodiment, a drug product can be enteric coated so that the drug product will pass through the stomach into the intestine prior to initiation of release.

Suitable coatings include ethylcellulose, polyvinylchloride, methylcellulose, polyurethane, cellulose acetate, polycarbonate, polyethylene, polypropylene, shellac and polymers of acrylic and methacrylic acids and esters of it.

The particle may be coated with one or more coatings, and the coatings may be the same or different, all to obtain the desired release kinetics. Interested readers are directed to the Hand Book of Pharmaceutical (2nd Edition., A. Wade & P.J.

Welker, Eds., American Pharmaceutical Assoc., Washington, D.C. 1994) for further detail, which is hereby incorporated by reference. Alternatively, the particle can be designed to give a predetermined sustained release profile (i.e., zero or first order release kinetics) from moment of ingestion. The appropriate materials for use as the delivery vehicle will be readily apparent to one skilled in the art.

The aspected particles of the invention may be incorporated into a bolus system (e.g., a sugar tablet permeated with the active to be delivered), which is formulated for immediate dissolution and release in the mouth. Such systems are used in place of swallowable tablets for those patients that can not tolerate tablets.

The disadvantage of this system is that it is not possible to achieve sustained delivery. However, the aspected particle of the present invention which has been formulated for sustained drug delivery may be incorporated into a bolus system to achieve controlled drug release. Thus, the sugar tablet is taken into the mouth by the patient where it dissolves, releasing the aspected drug-incorporated aspected particles of the invention. The aspected particles are then swallowed by the patient. The particles are non-gritty and have an acceptable mouth feel so that the patient can swallow them without a gagging reflex or unpleasant feeling in the mouth.

In other preferred embodiments, hydrogel coatings may be used to provide a controlled release of the drug. Hydrogel coatings may be used to coat the outer

surface of the aspected particle. Thus, the gel provides a physical barrier to diffusion of the drug, which slowly swells with water from the physiological environment. The water swollen coating permits drug diffusion. Where it is desired that the release rate be relatively slower, the hydrogel may be selected to be slow swelling. Conversely, where it is desired that the release rate be relatively faster, the hydrogel may be selected to be rapidly swelling. In yet another embodiment of the invention, the particle is coated with a rapidly swelling hydrogel. The rapid swelling and volume change of the coating is effective to disintegrate the particle, thereby providing substantially immediate drug delivery. Hydrogels having the above-noted swelling properties are well-known in the art.

These hydrogel coatings may be the same or different from those used as lubricious coatings described hereinabove. Thus, in one embodiment of the invention a single hydrogel layer is included which provides both a diffusion barrier for controlled drug delivery and a lubricious coating for improved mouth feel. In other embodiments of the invention, an inner coating is applied to control drug diffusion and an outer coating is used as the lubricious coating.

In other embodiments, a porogen may be included in the coating, which is water-soluble and which dissolves in water to generate pores in the membrane to permit the release of the drug from the core in an aqueous environment. The porogen may be selected from the group consisting of polyvinyl alcohol, polyvinylpyrrolidone, polyethyleneglycol, lactose, fumaric acid, citric acid, tartaric acid, sodium citrate, sodium bicarbonate, sodium fumarate, sodium carbonate, monosaccharides and disaccharides, hydroxypropylmethylcellulose, microcrystalline cellulose, polymers of acrylic and methacrylic acids, esters of polyurethane or polyvinylchloride, and potassium or sodium chlorides.

In other embodiments, an additive may be included in the coating which is enzymatically degradable and will degrade to generate pores in the membrane to permit the release of the drug from the core in the appropriate site at the gastrointestinal tract. The additive may be selected from compounds containing azo bonds, which will degrade in the lower gastrointestinal tract, (e.g., colon) in the presence of azo-reductase. Therefore the release will initiate only at the colon. For example, pectin is a suitable compound

In another aspect of the invention, the drug is incorporated into the particle as a solid dispersion. The solid dispersion may also include acid or base components in order to control the pH for optimal drug dissolution rates. Exemplary acid

components include adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid and tartaric acid, and base components include calcium carbonate, calcium hydroxide, magnesium hydroxide, sodium bicarbonate, sodium carbonate, sodium citrate and sodium hydroxide. The solid dispersion may include a surfactant component selected from sodium lauryl sulphate, a sodium carboxylate, an alkyl sulphate, a polyethylene glycol ester, a polyethylene ether, an ethoxylated sorbitan ester and an alkyl trimethylammonium halide and mixes.

A drug product formulated in this manner has the following advantages: it is easy to ingest as it is likely to stick into interstitial cavities of the mouth and as a result will not leave a residual sensation as spherical-shaped products do; it is relatively uniform in flow and handling characteristics for consumer appeal and ease of manufacturing; it possesses a controllable surface area to volume ratio to provide reproducible dissolution/release property compared with spherically shaped particles; it provides a controlled release kinetics that offset the short half-life of the active ingredient and thus does not require multiple dosages; it exhibits satisfactory stability; and it is sufficiently palatable and convenient, and has an acceptable mouth feel so as to ensure greater patient compliance over other current spherical-shaped products.

In another aspect of the invention, the particle may be incorporated into a semi-solid base to form a spoon-able drug delivery system. The semi-solid base may be comprised of pectin, guar gum, xanthan gum, gum arabic, gum acacia, locust bean gum, carageenan gum, alginate acid, psyllium hydrocolloid, oat bran gum, rice bran gum, glucomannan, tragacanth gum, karsya gum, tapioca, corn starch, cellulose gums, agar, gelatin, polyacrylates, polysaccharides, polyvinylpyrrolidone, pyrrolidones, polyols, collagen, polyethylene glycols, polyvinyl alcohols, polyethers, polyesters, natural or synthetic oils, liquid paraffin, beeswax, silicon waxes, natural or modified fatty acids, or combinations of thereof. Additionally viscous fruit purees such as apple, prune, apricot, pear, pineapple, banana, grape, strawberry, raspberry, blackberry, boysenberry, loganberry, dewberry, gooseberry, cranberry, mulberry,

elderberry, blueberry, fig, currant, kiwi may be used.

The invention may be applied to populations which experience difficulties in taking conventional solid and liquid dosage formats. For example, geriatric, pediatric, oncology patients or other patients who cannot swallow will benefit from a spoonable drug delivery dosage form. Similarly to the elderly, young children who cannot handle the swallowing of a tablet prefer a dosage form that could be spoon-fed to them. Cancer patients who undergo radiation therapy of the head and neck area or take chemotherapeutic drugs experience the lack of formation of saliva and/or esophagitis, which result in inability to take solid food such as tablets.

The active compounds that may be loaded into the drug delivery platforms of the present invention are any substances having biological activity, including proteins, polypeptides, polynucleotides, nucleoproteins, polysaccharides, glycoproteins, lipoproteins, and synthetic and biologically engineered analogs thereof.

Examples of biologically active compounds that might be utilized in a delivery application of the invention include literally any hydrophilic or hydrophobic biologically active compound. Preferably, though not necessarily, the drug is one that has already been deemed safe and effective for use by the appropriate governmental agency or body. For example, drugs for human use listed by the FDA under 21 C.F.R. 330.5, 331 through 361; 440-460; drugs for veterinary use listed by the FDA under 21 C.F.R. 500-582, incorporated herein by reference, are all considered acceptable for use in the present invention.

The term "biologically active compound" includes pharmacologically active substances that produce a local or systemic effect in animals, plants, or viruses. The term thus means any substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease or in the enhancement of desirable physical or mental development and conditions in an animal, plant, or virus. The term "animal" used herein is taken to mean mammals, such as primates, including humans, sheep, horses, cattle, pigs, dogs, cats, rats, mice; birds; reptiles; fish; insects; arachnids; protists (e.g. protozoa); and prokaryotic bacteria. The term "plant" means higher plants (angiosperms, gymnosperms), fungi, and prokaryotic blue-green "algae" (i.e. cyanobacteria).

The pharmaceutically active compound may be any substance having

biological activity, including proteins, polypeptides, polynucleotides, nucleoproteins, polysaccharides, glycoproteins, lipoproteins, and synthetic and biologically engineered analogs thereof. The term "protein" is art-recognized and for purposes of this invention also encompasses peptides. The proteins or peptides may be any

5 biologically active protein or peptide, naturally occurring or synthetic.

Examples of proteins include antibodies, enzymes, steroids, growth hormone and growth hormone-releasing hormone, gonadotropin-releasing hormone, and its agonist and antagonist analogues, somatostatin and its analogues, gonadotropins such as luteinizing hormone and follicle-stimulating hormone, peptide-T, thyrocalcitonin,

10 parathyroid hormone, glucagon, vasopressin, oxytocin, angiotensin I and II, bradykinin, kallidin, adrenocorticotrophic hormone, thyroid stimulating hormone, insulin, glucagon and the numerous analogues and congeners of the foregoing molecules.

Classes of pharmaceutically active compounds include, but are not limited to,

15 anti-AIDS substances, anti-cancer substances, antibiotics, immunosuppressants (e.g. cyclosporine) anti-viral substances, enzyme inhibitors, neurotoxins, opioids, hypnotics, antihistamines, lubricants, tranquilizers, anti-convulsants, muscle relaxants and anti-Parkinson substances, anti-spasmodics and muscle contractants, mitotics and anti-cholinergics, anti-glaucoma compounds, anti-parasite and/or anti-protozoal compounds, anti-hypertensives, analgesics, anti-pyretics and anti-inflammatory agents such as NSAIDs, local anesthetics, ophthalmics, prostaglandins, anti-depressants, anti-psychotic substances, anti-emetics, imaging agents, specific targeting agents, neurotransmitters, proteins, cell response modifiers, and vaccines.

A more complete listing of classes of compounds suitable for loading into polymers using the present methods may be found in the *Pharmazeutische Wirkstoffe* (Von Kleemann et al. (eds) Stuttgart/New York, 1987, incorporated herein by reference). Examples of particular pharmaceutically active substances are presented below:

20 Anti-AIDS substances are substances used to treat or prevent Autoimmune Deficiency Syndrome (AIDS). Examples of such substances include CD4, 3'-azido-3'-deoxythymidine (AZT), 9-(2-hydroxyethoxymethyl) guanine acyclovir(), phosphonoformic acid, 1-adamantanamine, peptide T, and 2',3' dideoxyxycytidine.

Anti-cancer substances are substances used to treat or prevent cancer.

Examples of such substances include methotrexate, cisplatin, prednisone, hydroxyprogesterone, medroxyprogesterone acetate, megestrol acetate, diethylstilbestrol, testosterone propionate, fluoxymesterone, vinblastine, vincristine, vindesine, daunorubicin, doxorubicin, hydroxyurea, procarbazine, aminoglutethimide,

5 methiobrelamine, cyclophosphamide, melphalan, uracil mustard, chlorambucil, busulfan, carmustine, lomustine, dacarbazine (DTIC), dimethyltriazenomidazolecarboxamide), melphalate, 5-fluorouracil, cytarabine, cytosine arabinoside, mercaptopurine, 6-mercaptopurine, thioguanine.

10 Antibiotics are art recognized and are substances which inhibit the growth of or kill microorganisms. Antibiotics can be produced synthetically or by microorganisms. Examples of antibiotics include penicillin, tetracycline, chloramphenicol, minocycline, doxycycline, vanomycin, bacitracin, kanamycin, neomycin, gentamycin, erythromycin and cephalosporins.

15 Anti-viral agents are substances capable of destroying or suppressing the replication of viruses. Examples of anti-viral agents include a-methyl-P-adamantane methylamine, 1,-D-ribofuranosyl-1,2,4-triazole-3 carboxamide, 9-[2-hydroxy-ethoxymethyl]guanidine, adamantananine, 5-iodo-2'-deoxyuridine, trifluorothymidine, interferon, and adenine arabinoside.

20 Enzyme inhibitors are substances which inhibit an enzymatic reaction.

Examples of enzyme inhibitors include edrophonium chloride, N-methylphysostigmine, neostigmine bromide, physostigmine sulfate, tacrine HCl, tacrine, 1-hydroxy maleate, iodotubercidin, p-bromotetramisole,

25 10-(alpha-diethylaminopropionyl)- phenolthiazine hydrochloride, calmidazolium chloride, hemicholinium-3, 3,5-dinitrocatechol, diacylglycerol kinase inhibitor I, diacylglycerol kinase inhibitor II, 3-phenylpropargylamine, N6-monomethyl-L-arginine acetate, carbidopa, 3-hydroxybenzylhydrazine HCl, hydralazine HCl, clorgyline HCl, deprenyl HCl, deprenyl HCl, D(+), hydroxylamine HCl, iproniazid phosphate, 6-MeO-tetrahydro-9H-pyrido-indole, niacinamide, pargyline HCl, quinacrine HCl, semicarbazide HCl, tranlycypromine HCl, N,N-diethylaminoethyl-2,2-diphenylvalerate hydrochloride,

30 3-isobutyl-1-methylxanthine, papaverine HCl, indomethacin, 2-cyclooctyl-2-hydroxy-

ethylamine hydrochloride, 2,3-dichloro- α -methylbenzylamine (DCMB),
 8,9-dichloro-2,3,4,5-tetrahydro-1H-2-benzazepine hydrochloride,
 p-aminogluthimide, p-aminogluthimide tartrate, R(+), p-aminogluthimide
 tartrate, S(-), 3-iodotyrosine, alpha-methyltyrosine, L-, alpha-methyltyrosine, D L-,
 5 acetazolamide, dichlorphenamide, 6-hydroxy-2-benzothiazolesulfonamide, and
 allopurinol.

Neurotoxins are substances which have a toxic effect on the nervous system,
 e.g. nerve cells. Neurotoxins include adrenergic neurotoxins, cholinergic
 neurotoxins, dopaminergic neurotoxins, and other neurotoxins. Examples of
 10 adrenergic neurotoxins include N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine
 hydrochloride. Examples of cholinergic neurotoxins include acetylcholine
 mustard hydrochloride. Examples of dopaminergic neurotoxins include
 6-hydroxydopamine HBr, 1-methyl-4-(2-methylphenyl)-1,2,3,6-tetrahydro-pyridine
 hydrochloride, 1-methyl-4-phenyl-2,3-dihydropyridinium perchlorate,
 15 N-methyl-4-phenyl-1,2,5,6-tetrahydropyridine HCl, 1-methyl-4-phenylpyridinium
 iodide.

Opioids are substances having opiate like effects that are not derived from
 opium. Opioids include opioid agonists and opioid antagonists. Opioid agonists
 include codeine sulfate, fentanyl citrate, hydrocodone bitartrate, loxeramide HCl,
 20 morphine sulfate, noscapine, norcodeine, normorphine, thebaine. Opioid antagonists
 include nor-binaltorphimine HCl, buprenorphine, chlornaltrexamine 2HCl,
 funaltrexamine HCl, nalbuphine HCl, nalorphine HCl, naloxone HCl, naloxonazine,
 naltrexone HCl, and naltrindole HCl.

Hypnotics are substances, which produce a hypnotic effect. Hypnotics
 25 include pentobarbital sodium, phenobarbital, secobarbital, thiopental and mixtures,
 thereof, heterocyclic hypnotics, dioxopiperidines, glutarimides, diethyl isovaleramide,
 α -bromoisovaleryl urea, urethanes and disulfanes.

Antihistamines are substances, which competitively inhibit the effects of
 histamines. Examples include pyrrolamine, chlorpheniramine, terahydrazoline, and
 30 the like.

Lubricants are substances that increase the lubricity of the environment into
 which they are delivered. Examples of biologically active lubricants include water

and saline.

Tranquilizers are substances, which provide a tranquilizing effect. Examples
 of tranquilizers include chlorpromazine, promazine, fluphenazine, reserpine,
 desipridine, and meprobamate.

5 Anti-convulsants are substances, which have an effect of preventing,
 reducing, or eliminating convulsions. Examples of such agents include primidone,
 phenytoin, valproate, Chk and ethosuximide.

Muscle relaxants and anti-Parkinson agents are agents which relax muscles or
 reduce or eliminate symptoms associated with Parkinson's disease. Examples of
 10 such agents include mephenesin, methocarbamol, cyclobenzaprine hydrochloride,
 trihexyphenidyl hydrochloride, levodopa/carbidopa, and biperiden.

Anti-spasmodics and muscle contractants are substances capable of preventing
 or relieving muscle spasms or contractions. Examples of such agents include
 atropine, scopolamine, oxyphenonium, and papaverine.

15 Miotics and anti-cholinergics are compounds, which cause bronchodilation.
 Examples include echothiophate, pilocarpine, physostigmine salicylate,
 diisopropylfluorophosphate, epinephrine, neostigmine, carbachol, methacholine,
 bethanechol, and the like.

Anti-glaucoma compounds include betaxalol, pilocarpine, timolol, timolol
 20 salts, and combinations of timolol, and/or its salts, with pilocarpine.

Anti-parasitic, protozoal and -fungals include ivermectin, pyrimethamine,
 trisulfapyrimidine, clindamycin, amphotericin B, nystatin, flucytosine, niamycin,
 and miconazole.

Anti-hypertensives are substances capable of counteracting high blood
 25 pressure. Examples of such substances include alpha-methyldopa and the
 pivaloyloxethyl ester of alpha-methyldopa.

Analgesics are substances capable of preventing, reducing, or relieving pain.
 Examples of analgesics include morphine sulfate, codeine sulfate, meperidine, and
 nalorphine.

30 Anti-pyretics are substances capable of relieving or reducing fever and
 anti-inflammatory agents are substances capable of counteracting or suppressing
 inflammation. Examples of such agents include aspirin (salicylic acid),

indomethacin, sodium indomethacin trihydrate, salicylamide, naproxen, colchicine, fenoprofen, sulindac, diflunisal, diclofenac, indoprofen and sodium salicylamide. Local anesthetics are substances, which have an anesthetic effect in a localized region. Examples of such anesthetics include procaine, lidocaine, tetracaine and dibucaine.

Ophthalmics include diagnostic agents such as sodium fluorescein, rose bengal, methacholine, adrenaline, cocaine, and atropine. Ophthalmic surgical additives include alpha-chymotrypsin and hyaluronidase.

Prostaglandins are art recognized and are a class of naturally occurring

chemically related, long-chain hydroxy fatty acids, which have a variety of biological effects.

Anti-depressants are substances capable of preventing or relieving depression. Examples of anti-depressants include imipramine, amitriptyline, nortriptyline, protriptyline, desipramine, amoxapine, doxepin, maprotiline, tranylcypromine, phenelzine, and isocarboxazide.

Anti-psychotic substances are substances, which modify psychotic behavior. Examples of such agents include phenothiazines, butyrophenones and thioxanthenes.

Anti-emetics are substances, which prevent or alleviate nausea or vomiting. An example of such a substance includes dramamine.

Imaging agents are agents capable of imaging a desired site, e.g. tumor, *in vivo*. Examples of imaging agents include substances having a label, which is detectable *in vivo*, e.g. antibodies attached to fluorescent labels. The term antibody includes whole antibodies or fragments thereof.

Specific targeting agents include agents capable of delivering a therapeutic agent to a desired site, e.g. tumor, and providing a therapeutic effect. Examples of targeting agents include agents which can carry toxins or other agents which provide beneficial effects. The targeting agent can be an antibody linked to a toxin, e.g. ricin A or an antibody linked to a drug.

Neurotransmitters are substances that are released from a neuron on excitation and travel to either inhibit or excite a target cell. Examples of neurotransmitters include dopamine, serotonin, γ -aminobutyric acid, norepinephrine, histamine, acetylcholine, and epinephrine.

Cell response modifiers are chemotactic factors such as platelet-derived growth factor (PDGF). Other chemotactic factors include neutrophil-activating protein, monocyte chemoattractant protein, macrophage-inflammatory protein, platelet factor, platelet basic protein, and melanoma growth stimulating activity. 5 epidermal growth factor, transforming growth factor (alpha), fibroblast growth factor, platelet-derived endothelial cell growth factor, insulin-like growth factor, nerve growth factor, and bone growth/cartilage-inducing factor (alpha and beta), or other bone morphogenetic protein.

Other cell response modifiers are the interleukins, interleukin inhibitors or 10 interleukin receptors, including interleukin 1 through interleukin 10; interferons, including alpha, beta and gamma; hematopoietic factors, including erythropoietin, granulocyte colony stimulating factor, macrophage colony stimulating factor and granulocyte-macrophage colony stimulating factor; tumor necrosis factors, including 15 alpha and beta; transforming growth factors (beta), including beta-1, beta-2, beta-3, inhibin, and activin; and bone morphogenetic proteins.

The aspected particle may be incorporated into a variety of architecture in order to obtain the desired release profiles. Exemplary fabrication methods and drug delivery vehicle architectures include the following.

Aspected particles may be prepared according to conventional methods. For 20 example, the drug and pharmaceutically acceptable excipients may be taken up into solution or may be made into a slurry. The solution or slurry may be cast against a flat surface and allowed to dry into a thin film. The film may be further cut or shredded into aspected particles of the desired dimensions. The films may be formed by air-drying, oven-drying, lyophilization and the like.

In another embodiment of the invention, the drug and pharmaceutically acceptable excipients may be taken up into a liquid to form a paste or dough-like mixture. The mixture may be forced through a screen having the appropriate 25 dimensions. The resulting particles may be dried as described hereinabove. The drug may be incorporated the aspected particles by microgranulation of the drug with suitable pharmaceutically acceptable excipients and then mixing the microgranular with another bases and coating polymers to form aspected particles and processing the mixture as described herein. 30

In another embodiment of the invention, the particles may be prepared using a spray drying technique (batch process). A drug solution (1 µg/mL - 5 mg/mL) containing acceptable pharmaceutical excipients may be sprayed on a rotating drum. The drum could be either warm or cooled to subambient. The system could be under reduced pressure (all these parameters are determined by the drug solubility and solvent volatility).

Particle size may be controlled by mechanical milling or cryomilling to reduce the solid mixture to the desired size (1 µm to 7 µm). The preferred range is 1 to 1000 µm, and more preferably 10 - 500 µm. The particles may be used as is or may be fractionated to the desired size distribution using mechanical screens. The desired fractions may be coated with a single or double coating using a Wurster Coater. In preferred embodiments, the first coat could be a time release coat while the second coat could provide a slip, a taste masking, a moisture barrier.

Milling of aspected particles may be accomplished using acceptable pharmaceutical processes. Thus, for example, the particles may be compressed between two rollers (when wet) followed by drying to form aspected particles.

In another embodiment of the invention, the aspected particles may be manufactured in a continuous process by spraying a polymeric solution containing the drug and optional excipients onto a moving belt (heated or cooled) to form a thin film, which can be dried and cut into particles. Alternatively, the process may be used to form laminate structures, for example, by first spray coating a film-forming layer, then applying a drug solution to the dried coating layer (in a non-miscible solvent for the coating layer). Thereafter, a final layer may be sprayed on to form a three-laminated product.

The film mono- or multi-laminate sheet may be reduced in size by mechanical mill or cryomill and blended to form uniform aspected particles (1 µm to 10 µm). Further, the aspected particles may be coated as described above to cover edges and/or to add additional desired properties such as to provide a slip, a taste masking or a moisture barrier.

In another embodiment of the invention, a liquid may be frozen to form the aspected particle. A cylindrical evaporator with a refrigerant circulation tubing

assembly between its inner and outer surfaces and having an axially driven rotatable shaft in the evaporator center is used. A nozzle on the shaft discharges liquid toward the evaporator inner surface, where it freezes as a sheet, and a blade on the shaft removes the frozen sheet as flakes.

A pharmaceutical preparation may be prepared free of organic solvents for oral administration which contains a meltable active ingredient for a delayed release of the meltable active ingredient and which includes forming a mixture consisting of the meltable active ingredient and a matrix forming auxiliary agent which is meltable and soluble in the active ingredient when the active ingredient is melted, pulling the mixture; and kneading the melt until a homogeneous uniform mass is obtained; and forming aspected microparticulates by rolling between rotating drums and mincing the sheet.

The aspected particles of the invention may also be prepared by extruding single or multi-layered thin films 30 incorporating the drug which is then shredded into aspected particles as illustrated in Figure 3A. The multi-layer laminated form contains a core layer 32 in which at least a major portion of the medicament is contained. The core layer consists is flanked by layers 34 containing either water-soluble polymers, water-insoluble polymers, or both, in order to obtain the desired release kinetics. The laminate aspected particle may also contain an outer protective-barrier membrane layer (not shown). Alternatively, the laminate particle may be made up of layers in which each has a difference composition, as shown in Figure 3B. This film is treated is shredded as previously described.

Aspected particles may be formulated as capsules, tablets or powders that may be added to water or other suitable liquid. The particles remain suspended in the liquid so that administration of the drug is accomplished as a drink, avoiding difficulties of swallowing or chewing tablets, or parenteral administration and therefore improving patient compliance. The aspected particles form a fine suspension in water before ingestion, reducing effects of food, presence of bile, and pH, especially on dissolution of sparingly soluble drugs. They prevent absorption in the oral cavity, and allow targeting of drug release at the required absorption site. Drug release can be controlled as described herein to give a therapeutic effect over a any desired time period, e.g., a 24-hour period for a once a day administration.

In the fabrication of fast-dissolving tablets, aspected particles may be incorporated into an effervescent matrix that dissolves in the mouth with or without additional water. The aspected particles then become available and slide easily down to the esophagus. Each aspected particle becomes a sustained release reservoir.

5 Current fast dissolving tablet technologies provide just immediate release and do not provide added benefits as for sustained release capabilities. See, for Example U.S. Patent No. 4,581,232. Alternatively, aspected particles may be formulated into capsules, tablets or powders that could be effervesce on addition of water or form suspensions once added to water (or juice).

10 In the fabrication of chewable tablets, aspected particles are incorporated into a tablet that could be chewed. Once chewed, the particles become available and slide easily down to the esophagus. Each aspected particle may function as a sustained release reservoir.

15 In other preferred embodiments, a composition is providing comprising a combination of sustained and rapid release. In one embodiment, aspected particulate formulations may be provided for once-daily oral administration in which the drug is formulated in aspected particle designed to release the drug at a rate such that therapeutically effective blood levels are maintained over 24 hours. The formulation includes a second portion formulated for prompt release to obtain a rapid therapeutic response.

20 Alternatively, a single particle could be made of a combination of fast and slow release. As an example, an aspected microparticulate comprising: (a) a core of drug or its salt, and an acceptable excipients surrounded by (b) a membrane, containing mostly a water insoluble, film forming synthetic polymers, with a minor amounts of water soluble synthetic polymers; and (c) a final layer of a rapid release form of drug, to provide effective therapeutic amounts immediate after administration.

25 In another embodiment of the invention an oral formulation for controlled absorption of drugs comprises aspected particulate having (1) a core 40 containing the drug, or its pharmaceutically acceptable salt, and (2) a membrane 42 of at least one film-forming polymer which controls the rate of the drug release into an aqueous medium, as is shown in Figure 4. The aspected microparticulate also could have a

pH-independent dissolution rate.

In another embodiment of the invention, an oral formulation controlled absorption of drugs comprises aspected microparticles having (1) a core 50 of swellable hydrogel that swells in response to stimuli or water, (2) a drug 52 or its pharmaceutically acceptable salt, and (3) a membrane 54 of at least one film-forming polymer which controls the rate of the drug release into an aqueous medium. The swellable hydrogel core will assist to push out the drug payload 56 in a controlled fashioned through the coating, as is illustrated in Figure 5.

10 In yet another embodiment of the invention, an oral formulation includes a swellable hydrogel, that swells in response to stimuli or water, located in the core of the aspected particle. The core swells in response to stimuli in order to prevent the decrease in the release rate towards the end of the diffusion process of the drug to the environment. The swellable gel core may be used in aspected particles with or without an outer coating used to promote mouth-feel or control drug delivery. It may also be used in aspected particles described above having a membrane of a film-forming polymer which controls the rate of release into an aqueous medium

15 Once the aspected particles pass the mouth, it may disintegrate in the stomach or gastrointestinal tract to the individual aspected or spherical granulars to increase the distribution over a wide surface area in the gastrointestinal tract. Poorly water-soluble drugs could be incorporated into polymeric films that could be manufactured into aspected particles. For example, polymers such as hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose phthalate, poloxamers or polyethyleneglycols (PEG). The drug could be solubilized or suspended in those polymers. One optional drug state would be of an amorphous state to enhance drug stability and drug solubility. In another method the drug could be crystalline and each crystal is coated separately. Disintegrants could be added to the aspected particle to precisely control the release kinetics. The disintegrants control the water uptake to a hydrophobic matrix and as a result effect the coating of the particle.

The aspected particle could be constructed from multilayers, as shown in

30 Figure 3. Where some layers contain drug and some layers may not contain drugs. The drug will release through the non-drug layers that will act to control the release

barriers. It would also allow the incorporation of a few different drugs into one particle in different layers. In other embodiments, the aspected particle could be constructed by forming an inner, inert core, as shown in Figure 5. Followed by coating the inner core with active pharmaceutical agent. Finally the unit is coated with another layer that could act as taste masking layer and or to control the release layer.

A sustained-release aspected particle includes an excipient or coating, and at least one pH adjuster selected from organic acid, organic acid salt, organic base, inorganic base and base salt. The excipient or coating composition surrounds a core comprising a medicament whose solubility varies with pH. The pH of the excipient or coating composition is adjusted to a desired pH to ensure that the rate of dissolution of the medicament is independent of the pH of the environment in which dissolution occurs.

A time-controlled explosion system in which drug release is caused by explosion of a membrane after a definite time period, said system comprising a preparation in the form of a aspected particles, said preparation comprising a core, a drug, swelling agent and an outer membrane of water-insoluble coating material.

Oral pharmaceutical preparations of aspected particles, which comprise a pharmacologically active drug, bound to small particles of an ion-exchange resin to provide a drug-resin complex having a drug content above a specified value. The drug-resin complex is subsequently coated with a water-permeable diffusion barrier coating that is insoluble in gastrointestinal fluids thereby providing a controllable sustained release of drug under conditions encountered in the gastrointestinal tract.

It is anticipated that the aspected particle may be used in conjunction with a wide variety of drugs. In particular, the aspected particle may be used in the controlled abortion of methyldopa. The aspected particle comprises (a) an aspected particle having a core of methyldopa (or its pharmaceutical salt) and an organic acid; and (b) a membrane or coating surrounding the core mainly comprising a pharmaceutically acceptable, film-forming, water-insoluble polymer. By controlling the number of coating layers permit a controlled release of methyldopa from the pellet. Rate of release over 24 hours after oral administration and is pH independent.

In another embodiment, the aspected particle is adapted to deliver diltiazem. A controlled absorption diltiazem formulation for oral administration includes:

aspected particles having a core of diltiazem or a its pharmaceutically acceptable salts. A membrane(s) or coating surrounds the core and contains a major amount of a pharmaceutically acceptable film-forming, water-insoluble polymer and a minor amount of a pharmaceutically acceptable film-forming, water-soluble polymer, the number of layers in the membrane and the ratio of the water soluble polymer to water-insoluble polymer being effective to permit release of the diltiazem from the aspected particle at a rate allowing controlled absorption thereof for 12 to 24 hours period following oral administration.

In another embodiment of the invention, an oral deliver vehicle is provided for delivery of verapamil. The formulation includes aspected particles consisting of a core including verapamil and a surrounding membrane or coating consisting mainly of pharmaceutically acceptable, film-forming water-insoluble polymer plus a small amount of a similar water-soluble polymer. The number of layers and the ratio of the water-soluble to water-insoluble polymers in the coating is chosen so that the drug is released at a rate which allows controlled absorption over 24 hr following oral administration, the preferred rate being measured *in vivo* would be T_{max} of 7-10 hr.

The aspected particles may be provided in the form of a gelatin capsule (or similar structure) so that the dosage form could be taken either as a whole or be opened and poured onto food or drink. The packaging may be designed to enhance the ease of opening, a feature particularly attractive to an aging patient population. By way of example, the aspected particles may be provided in a sachet. Thus, a single packaging design of the aspected particles, i.e., a capsule, may be either ingested as an intact capsule or opened and administered as an additive in liquids or other suitable bases.

In yet a further example of the invention, an oral drug delivery vehicle for administering includes a sealable container including a removable seal for holding and storing a desired dose of the pharmaceutically active agent as an aspected particle in a stable condition until needed and a base which is sweetened, flavored and colored to produce a mixture that is palatable and pleasing to the taste. The

1. An oral delivery vehicle, comprising:
an aspected particle including a pharmaceutically active component and
excipients, wherein the vehicle is formulated and/or constructed and arranged to
provide controlled delivery of the pharmaceutically active component.

5

2. An oral delivery vehicle, comprising:
an aspected particle including a pharmaceutically active component and
excipients, the aspected particle having one dimension that is about an order of
magnitude smaller than the other two dimensions.

10

3. An oral delivery vehicle with an acceptable mouth-feel, comprising:
an aspected particle including a pharmaceutically active component and
excipients, the aspected particle having one dimension that is about an order of
magnitude smaller than the other two dimensions; and
a lubricious coating on the particle.

15

4. The delivery vehicle of claim 1, wherein controlled delivery is attained
by coating the particle.

20

5. The delivery vehicle of claim 4, the coating is selected as a diffusion
barrier to control drug delivery.

6. The delivery vehicle of claim 4, wherein the coating is selected as a
barrier being impermeable to diffusion under a first set of environmental conditions,
and permeable to diffusion under a second set of environmental conditions.

25

7. The delivery vehicle of claim 6, wherein the environmental condition is
selected from the group consisting of temperature, pH, ionic strength and particular
molecules.

30

8. The delivery vehicle of claims 1, 2 or 3, further comprising
a base having a consistency capable of being spoon-fed and capable of ingestion

29

by a patient, the delivery vehicle being disposed therein.

9. The oral delivery vehicle of claim 8, wherein the base may be final or
non-food.

5

10. The oral delivery vehicle of claim 8, further comprising:
a sealable container including a removable seal for holding and storing the
aspected particles in a stable condition until needed, wherein the aspected particles and
the base are sealed inside the container.

10

11. The oral delivery vehicle of claim 8, wherein the base is sweetened,
flavored and colored to produce a base that is palatable and pleasing to the taste.

12. The delivery vehicle of claim 3, wherein the lubricious coating is a
hydrophobic coating.

15

13. The delivery vehicle of claim 12, wherein the hydrophobic coating is
selected from the group consisting of silicone oils, siloxanes and ethyl acetate.

20

14. The delivery vehicle of claim 3, wherein the coating is a hydrophilic
coating.

15. The delivery vehicle of claim 14, wherein the hydrophilic coating is
selected from the group consisting of polyvinyl alcohols (PVA), polyvinylpyrrolidone
(PVP), polyacrylic acids (PAA), poly(N-vinyl lactams), polyethylene oxides, polyvinyl
ethers and derivatives thereof.

25

16. The delivery vehicle of claim 3, wherein the coating swells to become
lubricious in the presence of an aqueous medium.

30

17. The delivery vehicle of claim 1, further comprising:
a lubricious coating on the outer surface of the aspected particle selected to

30

mixture and the aspected particles are sealed inside the container. The medication is in a aspected particle form and a delivery medium are stored in a chambered container separated by a rupturable membrane which is ruptured to mix the container contents.

5 These an other embodiments of the invention are illustrated by way of the examples which are provided for the purpose of illustration only and which are not intended to be limiting of the invention.

Example 1. L-DOPA (Sigma, Lot 55110565, 1.01 g); sucrose (2.04 g) and purified water (E-Pure, 1.5g) were mixed together. The semisolid mixture was stirred until it became homogeneous and spread on a glass plate and dried at 70 °C overnight. The product was ground to particles of roughly 1 X 1 X 0.1 mm in dimensions. Half of these particles were dipped in 4% solution of ethylcellulose (Benece) in methyl alcohol (Malinkrodt, Lot 3016KVRG) and air dried.

The aspected particles were placed in phosphate buffer saline solution, pH 7.4 at 37 °C and the solution was analyzed at given time points for the presence of L-DOPA by UV at 287 nm. We obtained an almost linear release of the L-DOPA over 24 hours. There was minimal difference in the release kinetics between the coated and the non-coated aspected particles. In this example the water soluble excipient (sucrose) influenced the release kinetics of the water insoluble drug.

20 Example 2. L-Dopa (Sigma, Lot 55H0565, 0.2089 g); ethylcellulose (Benece, Hercules, Lot FP10 13415), 0.3009 g); Avicel (FMC, Lot M723C, 0.4996 g) and purified water (E-Pure) were mixed together. The semisolid mixture was stirred until it became homogeneous and was spread on a glass plate and dried at 70 °C for 4 hours. The product was cut to small square aspected particles of roughly 1 X 1 X 0.1 mm in dimensions. Half of these particles were dipped in 4% solution of ethylcellulose (Benece) in methyl alcohol (Malinkrodt, Lot 3016KVRG) and dried.

The aspected particles were placed in phosphate buffer saline solution pH 7.4 at 37 °C and were analyzed at given time points for the release of L-DOPA by UV at 287 nm. We obtained a zero order release kinetics for the L-Dopa over 24 hours. The coated particles released 26% of the incorporated L-Dopa while the non-coated particles released 76% of the incorporated L-Dopa over that time period. In this example the water insoluble excipient influenced the release kinetics of the water

insoluble drug and the kinetics was further affected by the coating

Example 3 Benece (Hercules, Lot FP10 1345, 0.57 g), Avicel (FMC, Lot M723C, 0.81 g), Magnesium stearate (Malinkrodt, Lot 2256KVVD, 0.13 g) were mixed and purified water (4.9g) was added to form a dough-like mixture. The resulting semi-solid was spread into a screen with 1 X 1 mm opening and placed in a 65 °C oven for 1 h. The dried solid was pushed from the screen to form aspected particles. These particles were divided into three parts: 1/3 of the particles were left as is; 1/3 were coated with a 1.4% Carbolopol® solution (poly(acrylic acid), BF Goodrich, Lot CC769F88704) containing 1.4% banana flavor (Frontier); and 1/3 were coated with 1.3% Carbolopol solution containing 1% PEG 600 (Union Carbide, Lot IS781428) and 1.4% banana flavor. The particles were blind-tasted for their organoleptic feel: the uncoated group felt hard and gritty; the Carbolopol coated particles were a bit hard initially and become lubricious; the particles coated with both Carbolopol and PEG were lubricious and pleasant tasting from the start. In this example the coating with fast swelling hydrogel improved the organoleptic feel of the aspected particle.

Example 4 Phenylpropanolamine (Sigma, Lot 75F0551, 0.20 g); ethylcellulose (Benece, Hercules, Lot FP10 13415), 0.30 g); Avicel (FMC, Lot M723C, 0.36 g) and magnesium stearate (Malinkrodt, Lot 2256KVVD, 0.01g) were mixed to form a homogeneous solid mixture. Purified water (E-Pure, 2.1 g) was added and mixed together to form a dough like consistency. The semisolid mixture was spread on a glass slide and freeze dried overnight. The dry product was cut to small square aspected particles of 2 X 2 X 0.1 mm in dimensions. 1/2 of these particles were dipped in 0.3% solution of ethylcellulose (Benece) in methyl alcohol (Malinkrodt, Lot 3016KVRG) and 1/2 left as is.

The aspected particles were placed in phosphate buffer saline solution pH 7.4 at 37 °C and were analyzed at given time points for the release of Phenylpropanolamine by UV at 256 nm. In this example the coating retarded the release of a highly water soluble drug phenylpropanolamine.

Particle	t _{50%}	t _{90%}
Uncoated	-	50 min
Coated particles	1 h	8 h

What is claimed is:

enhance mouth-feel.

WO 99/30671

1/2

PCT/US98/26628

18 The oral delivery vehicle of claim 1, wherein the controlled drug delivery is attained by selection of appropriate excipients.

19 The oral delivery vehicle of claim 1, wherein the aspected particle is a laminate structure having a core layer comprised of the pharmaceutically active component and outer layers selected to control the delivery of the component from the core layer.

20 The oral delivery vehicle of claim 19, further comprising:

a lubricious coating on the outer surface of the aspected particle selected to enhance mouth-feel.

21 The oral delivery vehicle of claim 1, wherein the aspected particles are incorporated into a tablet, capsule, fast dissolving tablet or chewable tablet.

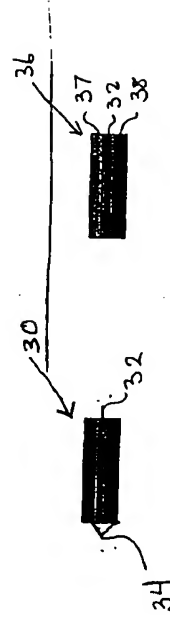
22 The oral delivery vehicle of claim 1, wherein the aspected particles are incorporated into a capsule configured and arranged to permit opening of the capsule prior to administration to a patient.



Figure 1



Figure 2



3A

3B

Figure 3.



Figure 4

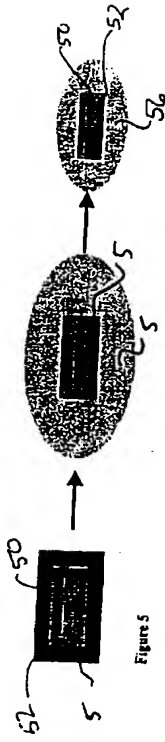


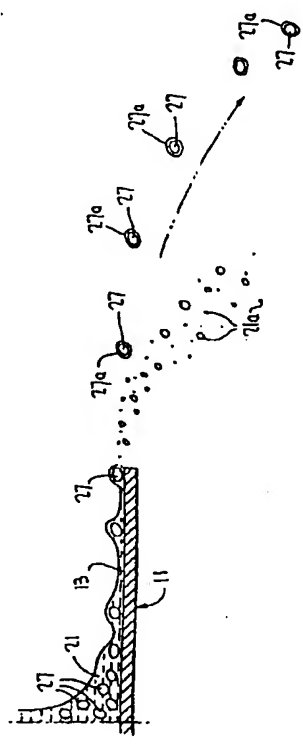
Figure 5



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(54) Title: METHOD AND APPARATUS FOR COATING PARTICLES OR LIQUID DROPLETS



(57) Abstract

Solid particles or viscous liquid droplets of core material (27) are encapsulated in a coating material (21) largely as single particles with a single coherent coating, by feeding a suspension of the two materials onto a rotating surface (11). The suspension is centrifugally dispersed by the rotating surface into relative large coated particles (27, 27a) and relatively small droplets (21a) of coating material. Only the size of the droplets of unused coating corresponds to the droplet formed from atomization of the liquid coating material. The size of the coated particles depends on the size of the uncoated particles and is much less dependent upon the atomization characteristics of the rotating surface. Upon being thrown from the rotating surface, or falling from that surface, the droplets (21a) and coated particles (27, 27a) are solidified by exposure to air and are separated by sieving, or the like. The solidified droplets of pure coating material may be recycled into the suspension. Coating of all particles is achieved by dispersing the individual components of core material in the coating material before the resulting suspension reaches the rotating surface.

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METHOD AND APPARATUS FOR COATING PARTICLES OR LIQUID DROPLETS

Abstract:

178a Abstract of WO8505288

Solid particles or viscous liquid droplets of core material (27) are encapsulated in a coating material (21) largely as single particles with a single coherent coating, by feeding a suspension of the two materials onto a rotating surface (11). The suspension is centrifugally dispersed by the rotating surface into relative large coated particles (27, 27a) and relatively small droplets (21a) of coating material. Only the size of the droplets of unused coating corresponds to the droplet formed from atomization of the liquid coating material. The size of the coated particles depends on the size of the uncoated particles and is much less dependent upon the atomization characteristics of the rotating surface. Upon being thrown from the rotating surface, or falling from that surface, the droplets (21a) and coated particles (27, 27a) are solidified by exposure to air and are separated by sieving, or the like. The solidified droplets of pure coating material may be recycled into the suspension. Coating of all particles is achieved by dispersing the individual components of core material in the coating material before the resulting suspension reaches the rotating surface.

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1 the present invention relates to improvements in such
2 methods and apparatus which provide encapsulation
3 techniques and effects which are unprecedented in the
4 prior art.

5 2. Discussion of the Prior Art

6 Coating or microencapsulation of solid particles
7 or liquid droplets is widely employed to protect coated
8 substances from environmental effects and/or control
9 their release time and/or confer improved handling
10 characteristics. Typical products which are coated or
11 microencapsulated are drugs, pesticides, dyes, etc..

12 Numerous coating or microencapsulation techniques
13 have been employed in the prior art, many of which are
14 described in the Encyclopedia Of Chemical Technology,
15 third edition, volume 15, pages 470-493 (1981), John
16 Wiley and Sons. By and large, these techniques suffer
17 from one or more important disadvantages, including:
18 high cost; inapplicability for coating particles smaller
19 than 200 micrometers in diameter; complexity; long
20 contact time between the core and coating materials prior
21 to solidification of the coating material; inability to
22 achieve wetting and coating of the core particles with
23 the desired coating material; inefficient separation of
24 coated particles from unused coating material and

1 inefficient usage or wastage of coating material. Also
2 important in many methods are the tendency for the coated
3 particles to agglomerate and the limited choice of wall
4 materials. There are severe cost disadvantages to most
5 methods because they are batch processes difficult to
6 operate on large commercial scale and because they must
7 employ a solvent for the coating and are unable to use
8 melted coating materials, which require no solvent
9 removal or handling facilities.

10 There have been a number of attempts in the prior
11 art to provide coating techniques which are devoid of the
12 aforesaid disadvantages. For example, in U.S. patent
13 number 4,386,895 (Sodickson), there is disclosed a
14 rotating apparatus having radially-extending conduits
15 from which hollow needles project radially outward into a
16 reservoir of jelling material. As the apparatus spins,
17 liquid core material is urged by centrifugal force
18 through the conduits and needles. The liquid core
19 material is formed into droplets at the distal ends of
20 the needles, and the droplets are centrifugally thrown
21 into a layer of the gelling material which forms on the
22 outer reservoir wall due to the centrifugal forces
23 produced by rotation. The droplets of liquid core
24 material are thusly encapsulated by the gelling
25 material. This technique works well for its intended

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METHOD AND APPARATUS FOR COATING
PARTICLES OR LIQUID DROPLETS

BACKGROUND OF THE INVENTION

1. Technical Field

The present invention relates to a method and apparatus for coating or microencapsulating solid particles or viscous liquid droplets. More particularly,

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1 purpose. However, it is limited to use with liquid as a
 2 core material (i.e., it cannot be used to
 3 microencapsulate solid particles) and the minimum size
 4 droplet that can be coated depends upon the inner
 5 diameter of the needle. As to the latter limitation,
 6 there are practical limitations on minimum needle size,
 7 particularly when viscous core liquids must flow
 8 therethrough.

9 In U.S. patent number 2,955,956 (Baugh et al.), a
 10 rotating disc or table is disposed below a feed pipe
 11 through which a slurry composition of coating material is
 12 fed. The slurry is spread over the spinning disc surface
 13 to form a thin film of the coating material thereon. An
 14 annular flow of solid granules is permitted to impinge
 15 upon the film on the disc surface, whereupon the granules
 16 are coated with the coating material. The coated
 17 granules are thrown or are permitted to fall from the
 18 rotating disc and are solidified by dry warm gas directed
 19 at the falling granules. A second annular flow of
 20 granules is directed onto the rotating film to scavenge
 21 the unused film and assure that all of it is utilized.
 22 Again, this technique is satisfactory for a limited
 23 purpose, namely coating granules, such as salt, with
 24 additives, but it cannot be readily employed to coat
 25 liquid droplets. Moreover, since the granules in the

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1 scavenging outermost annular flow cannot possibly be
 2 coated to the same extent as granules in the innermost
 3 flow, it is not possible with this technique to achieve
 4 uniform coating of all of the granules. Therefore, the
 5 Baugh et al. technique is more suitable for wide
 6 dispersion of additives onto the surface of granules than
 7 it is for coating particles.

8 British Patent No. 1,090,971 to Wilson, et al.,
 9 discloses a method of microencapsulating solid particles
 10 by forming a dilute suspension of the particles in a
 11 dilute solution of a resinous coating material in a
 12 volatile liquid, causing the suspension to impinge on a
 13 spinning disc whereby the dilute suspension is dispersed
 14 as a spray consisting of atomized coating solution and
 15 microencapsulated particle droplets, the spray of
 16 droplets then being exposed to steam at temperatures
 17 above the boiling point of the coating solvent which
 18 volatilizes the unwanted liquid solvent so as to leave
 19 coated particles plus particles of pure coating of the
 20 same size. The process, however, requires a feedstock
 21 solution having a very low percentage content of
 22 particles to be coated, involves the high temperature
 23 removal of a large amount of unused feedstock liquid by
 24 volatilization, and does not permit separation by sizing
 25 of coated particles from particles of pure coating
 26 material.

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Objects and Summary of the Invention

It is therefore an object of the present invention to provide an improved method and apparatus for coating or microencapsulating both solid particles and viscous liquid droplets.

It is another object of the invention to provide a method and apparatus for microencapsulating particles which enables at least a majority of the particles to be coated individually or discretely rather than in clusters while simultaneously providing improved means for separating unwanted and unused liquid coating material from the coated particles. More particularly, it is an object of the invention to provide a coating process and apparatus which includes controlled mechanical or physical separation of coated particles from unused liquid coating material by size discrimination, whereby the method is equally applicable to the coating of solid or viscous liquid particles, either with materials including a liquid solvent or with molten coating liquids, and whereby the wettability of the core particles or droplets by the coating material is relatively unimportant, permitting use of the method for a wider variety of core particles and coating materials.

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It is another object of the present invention to provide a method and apparatus for coating or microencapsulating solid particles and viscous liquid droplets over a wide range of particle and droplet sizes, including droplets and particles having diameters well below 200 micrometers.

It is a further object of the present invention to provide a method and apparatus for coating or microencapsulating solid particles or viscous liquid droplets with much less complexity, continuously, at a much faster rate, and at lower cost than is possible in much of the prior art, and to avoid the problem of agglomeration of the particles being coated.

Still another object of the present invention is to provide a method and apparatus for coating or microencapsulating solid particles or viscous liquid droplets wherein coating material can be easily re-cycled back into the process if not used during a first pass through the process.

It is yet another object of the present invention to provide a method and apparatus for coating or microencapsulating solid particles or viscous liquid

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1 droplets in which coating thickness can be easily
2 adjusted by adjustment of any of plural process
3 parameters.

4 A further object of the present invention is to
5 provide a method and apparatus for coating or
6 microencapsulating solid particles or viscous liquid
7 droplets wherein the contact time between the core and
8 coating materials prior to solidification of the coating
9 material can be made sufficiently short to prevent
10 degradation of some labile materials, or to prevent their
11 dissolving one in the other when they are partially or
12 totally miscible.

13 The present invention provides, in a process for
14 coating particles with a liquid coating, a method for
15 obtaining individually coated particles while
16 simultaneously facilitating removal of the coated
17 particles from excess coating liquid with which the
18 particles are mixed in a suspension, the method
19 comprising feeding the suspension onto a rotating surface
20 to separate the suspension into coated particles and
21 atomized liquid droplets expelled circumferentially from
22 the surface, and rotating the surface at a speed yielding
23 a predominance of the droplets of undesired liquid
24 coating of a predetermined size which is smaller than the
25 size of the coated particles.

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1 Thus in accordance with the present invention,
2 solid particles or liquid droplets of core material to be
3 coated are initially dispersed in molten or dissolved
4 coating material to form a suspension. The suspension of
5 the two materials is then fed to the surface of a
6 rotating disc, table or other rotating element. The
7 process parameters, particularly the speed of rotation of
8 the disc or other rotating element are controlled so that
9 the centrifugal forces imposed on the suspension by the
10 disc or the like cause the suspension to spread towards
11 the disc periphery with progressive thinning out of the
12 liquid and separation of excess coating material from the
13 coated particles, with dispersion of the suspension into
14 (1) large coated particles and (2) significantly
15 smaller-size atomized droplets of excess coating material
16 which are formed by atomization of the thin film of
17 liquid coating at the periphery of the disc or the like.
18 Thus, in accordance with the invention, the disc or the
19 like is used as a means for mechanically or physically
20 separating the excess coating liquid from the
21 individually coated particles and dispersing the
22 separated liquid as atomized droplets of significantly
23 smaller size than the coated particles. Most
24 importantly, to obtain the required separation and
25 dispersion, the invention involves relating the rotary
26 speed of the disc to the required size of atomized

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1 droplets of excess liquid coating material to be obtained
2 from the disc, rather than relating the disc speed to the
3 size of coated particles to be obtained. This represents
4 a significant departure from known techniques involving
5 the use of a rotating wheel or the like to provide
6 dispersion of coated particles, where the wheel speed is
7 related to the required size of coated particle
8 products. In practical terms, for coated particles of
9 comparable dimensions, the invention involves rotary disc
10 speeds surprisingly in excess of those used in the prior
11 art techniques.

12 The average mean size required for the atomized
13 droplets of excess coating liquid may, in practice, be
14 determined by the amount of contamination, i.e., excess
15 unused coating material, which is acceptable in the final
16 product of coated particles, such determination being
17 effected by known techniques involving the relative sizes
18 of the coated particles and the particle size
19 distribution characteristics of unused coating liquid,
20 related to rotational speeds, liquid feed rate, length of
21 wetted periphery, and viscosity in rotary atomizer-type
22 equipment. Typically, in accordance with the invention,
23 the average size of atomized droplets may be about 20% to
24 75% of the size of the coated particles.

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1 Since the materials being coated are solid (or
2 viscous liquid), they are not atomized but are simply
3 thrown from the disc as relatively large particles
4 retaining a coating of the liquid in which they were
5 immersed. The control of the process parameters to
6 provide separation of the suspension by the rotary disc
7 into individually coated particles and significantly
8 smaller droplets of excess coating material
9 differentiates the process of the present invention
10 completely from prior art processes such as spray
11 congealing, in which a slurry of dispersed solids is
12 atomized as a liquid, with the product solid present
13 inside the atomized droplets. In spray congealing the
14 dispersed solids are sufficiently finely divided that
15 there are many solid particles in most of the atomized
16 slurry product, and the size distribution of the entire
17 product approximates that predicted from atomization
18 correlations. In spray congealing, when the suspension
19 must behave as a liquid during atomization and no solvent
20 is subsequently removed, the volume fraction of solids in
21 the suspension (and hence, also in the product congealed
22 droplets) has an upper limit near 30%, while in the
23 present invention the volume fraction of coated solids in
24 the product particles may be in excess of 90%, owing to
25 the separation of the unused coating liquid on the
26 rotating disk and its atomization into smaller, easily

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1 removed particles. In the present invention essentially
 2 all of the solids in the feed slurry and all of the
 3 coated product solids are larger than the sizes predicted
 4 from atomization correlations for the processing
 5 conditions employed. An example of the size distribution
 6 of the feed solids, product solids and atomized coating
 7 obtained is provided in Example VII.

8 The invention further has clear distinctions from
 9 the old art of spray-chilling, in which a suspension is
 10 atomized with subsequent solidification of the droplets
 11 by cooling, and from spray-drying, in which a solvent is
 12 present in the original suspension or solution and is
 13 subsequently removed. In both these known processes, the
 14 feed suspension or solution is atomized as a liquid, and
 15 the products of the processes are the solidified
 16 droplets, and there is no separation between particles
 17 containing solids and those not containing solids. In
 18 principle any atomization device can be used which will
 19 give the desired droplets. In the present invention, the
 20 process variables are adjusted to give a completely
 21 different result, and products can be formed which are
 22 impossible to form in general spray-chilling or
 23 spray-drying. For example, it is convenient with the
 24 process invention to place thin waxy coatings (e.g. 100
 25 micrometers) around solid particles 2 millimeters in

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1 diameter. In spray-chilling, it would not be possible to
 2 pass the feed slurry through a pressure nozzle or
 3 two-fluid nozzle, because the core particles would block
 4 or plug the orifices in typical nozzles. If a very large
 5 nozzle was used to permit the particles to pass, the
 6 resultant coarse spray would include many product
 7 particles containing no core (just large drops of
 8 coating), a few core particles having thin coating, many
 9 having thick coating and many in agglomerates rather than
 10 as single coated particles. This would occur because
 11 particle formation in these orifice devices occurs by
 12 atomization of the entire slurry simply as a liquid which
 13 happens to contain some solid particles. Such a slurry
 14 of large particles could, of course, be passed over a
 15 rotating-disc atomizer without any plugging or flow
 16 stoppage. However, the disc would be run to treat the
 17 slurry as a simple fluid, giving all atomized droplets in
 18 the same size range. Again, this means that much of the
 19 coating would be in the form of particles as large as the
 20 coated particles and many of the particles will be in the
 21 form of agglomerates. In none of these cases could most
 22 of the unused coating be separated from the coated
 23 particles by simple means such as sieving, and the
 24 product would contain large inert particles of coating as
 25 a major fraction. This is unacceptable in most practical
 26 cases.

1 By contrast, in the present invention, with a feed
2 slurry containing e.g. 500 micron core particles, and a
3 desired coated product particle of 600 micron average
4 diameter, the disc size, rotational speed, feed rate of
5 the slurry and coating viscosity will be adjusted to
6 force all the unused coating to be in the form of
7 droplets much smaller (e.g. a mean diameter around 250
8 micrometers) so that most of it can be easily separated
9 from the product, and the product particles will
10 essentially be all in the form of single coated core
11 particles nearly all having an average coating thickness
12 of 50 microns. If it is desired, it is possible to make
13 the unused coating particles smaller, or somewhat larger,
14 while making the desired product.

15 A key point of the invention is to run the process
16 differently from a typical spray-chilling process. In
17 the latter process, the atomization is set to treat all
18 the feed slurry as a liquid, making droplets in the
19 desired size range. In the process invention, all
20 parameters are adjusted to force all unused particles
21 into a relatively small size, formed by atomization of
22 the film of pure coating, while the large product of
23 coated core particles is thrown off the disc surrounded
24 by the desired amount of remaining liquid, subsequently
25 solidified as a coating.

1 The small coating material droplets and the
2 coating-wetted particles resulting from operating the
3 disc in accordance with the invention are thrown or
4 caused to fall from the spinning surface and solidify due
5 to the drying or cooling effect of the surrounding air or
6 gas. Sieving or other size discrimination techniques
7 may be readily employed to remove the coated particles
8 from the much smaller particles of unused coating
9 material and the removal step is facilitated compared
10 with prior art processes because of the size
11 discrimination between the coated particles and the
12 smaller particles of excess coating material which is
13 conferred by the process invention. The coating material
14 particles thusly collected may be re-cycled into the
15 process. The minimum size of the solid particles or
16 liquid droplets which can be coated by this technique is
17 limited only by the size of the particles or droplets
18 themselves and by the lower limit of droplet size of
19 excess coating liquid which can be obtained with a
20 rotating disc (dry particles of 1-5 micrometers at high
21 disc speeds with low viscosity coatings containing
22 solvent). By completely dispersing the particles or
23 droplets in the molten coating material before the
24 materials are placed in contact with the rotating
25 surface, it is possible to coat all particles in a
26 similar fashion. The more uniform the size of the

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1 dispersed particles the more particle-to-particle
2 uniformity there will be in the coated particles. This
3 has little effect on the size distribution of smaller,
4 atomized excess coating.

5 Brief Description of the Drawings

6 These and other objects, features and many of the
7 attendant advantages of the present invention will be
8 better understood upon a reading of the following
9 detailed description considered in connection with the
10 accompanying drawings wherein like parts in each of the
11 several figures are identified by the same reference
12 numerals, and wherein:

13 Fig. 1 is a diagrammatic illustration of apparatus
14 according to the present invention which may be employed
15 to perform the method of the present invention;

16 Fig. 2 is a diagrammatic illustration of an
17 alternative embodiment of the present invention;

18 Fig. 3 is a diagrammatic representation of still
19 another embodiment according to the present invention;

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1 Fig. 4 is a diagrammatic representation of a
2 further embodiment employed in accordance with the
3 present invention;

4 Fig. 5 is a diagrammatic illustration of yet
5 another embodiment of the present invention;

6 Fig. 6 is a diagrammatic elevational view of a
7 rotary separating element showing its effect on a liquid
8 suspension when used in accordance with the invention;

9 Fig. 7 is a diagrammatic plan view of the element
10 shown in Fig. 6;

11 Fig. 8 is a view similar to Fig. 7 but showing
12 another type of rotary separating element;

13 Figs. 9, 10 and 11 are diagrammatic views of prior
14 art products (from a spray drying process) including
15 coated particles, the figures representing successive
16 stages in a coating process;

17 Fig. 12 is a view similar to Fig. 9 showing an
18 intermediate product according to the invention prior to
19 final separation of coated particles from droplets of
20 excess coating liquid; and

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1 Figs. 13 to 15 are diagrammatic views of
2 alternative rotary separating devices useful in
3 performance of the invention.

4 Description of the Preferred Embodiments

5 Referring specifically to Fig. 1 of the
6 accompanying drawings, an enclosed spray chamber 10 (with
7 only top wall 12 illustrated in Fig. 1) is provided for
8 performing the method of the present invention. Within
9 chamber 10 there is disposed a rotatable disc or table 11
10 having an upper surface 13 which may be disposed
11 horizontally. Rotatable disc 11 is rotatably driven
12 about its central vertical axis by means of a variable
13 speed drive motor 17 acting through drive shaft 15. A
14 speed control unit 19 permits adjustment of the
15 rotational speed of the disc 11.

16 Speed control 19 and motor 17 may be located
17 inside or outside of chamber 10, depending upon the
18 particular application. The disc may be disposed above
19 the motor or suspended below the motor, with appropriate
20 modification of feed lines, supports, etc.

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1 A reservoir 20 is adapted to contain molten or
2 dissolved coating material 21. The reservoir 20 is
3 heated, for example, by means of a heating coil 23
4 disposed about the reservoir periphery, to maintain the
5 coating material 21 in molten or dissolved form. In this
6 regard, the coating material 21 may be supplied to
7 reservoir 20 in molten form and maintained in that state
8 by means of the heating coil; alternatively, the coating
9 material may be supplied to the reservoir in solid form
10 and melted by the heat derived from heating coil 23. In
11 either case, the molten coating material 21 in the
12 reservoir is in a flowable state. A feed funnel 25 is
13 provided to extend through an opening in chamber 10 so as
14 to deliver individual mass components 27 of core material
15 (e.g., solid particles of core material) to be coated
16 into reservoir 20. In instances where the core material
17 is in the form of droplets of viscous liquid, funnel 25
18 may be replaced by a droplet-forming tube, a means of
19 feeding an emulsion or the like. A stirrer mechanism
20 extends into the chamber 10 and reservoir 20 and is
21 actuated by a variable speed stirrer motor 30 disposed
22 outside of chamber 20. The stirrer 22, when driven by
23 motor 30, acts to disperse the solid particles 27 (or
24 liquid droplets) of core material throughout the molten
25 coating material 21. The result is a slurry or
26 suspension of the two materials disposed in reservoir

1 20. This slurry or suspension is delivered through a
 2 gravity-feed passage 31, extending from the bottom of
 3 reservoir 20, to a ball valve mechanism 33. The ball
 4 valve 33 is selectively actuatable from outside chamber
 5 10 by means of actuating rod 35 to control the rate of
 6 flow of the suspension material through the ball valve
 7 33. It is noted that the heating coil 23 is disposed so
 8 as to heat the suspension as it passes through passage
 9 31 and ball valve 33, thereby assuring that the coating
 10 material remains in its molten state while in these
 11 components. The outlet passage 37 from ball valve 33 is
 12 disposed directly above the axial center of surface 13 so
 13 as to deliver the suspension material substantially along
 14 the rotation axis of disc 11.

15 The space above surface 13 is heated, for example,
 16 by means of industrial grade heat guns 39, to maintain
 17 the temperature on surface 13 sufficiently high so that
 18 the coating material in the suspension remains molten.
 19 Additional heat is provided at the underside of disc 11,
 20 for example, by means of infrared heat lamps 40. Heating
 21 may be provided by many methods such as preheated air,
 22 steam, radiant energy, induction heating, etc.

1 The top surface 13 of disc 11 may be smooth or may
 2 be provided with a plurality of angularly-spaced
 3 radially-extending grooves 24 defined therein, or raised
 4 fins, so as to establish paths of travel for the material
 5 deposited on surface 13 from ball valve 33. Grooved or
 6 vaned surfaces are advantageous if the particles to be
 7 coated are small, for example below 200 micrometers in
 8 diameter, and the coating is viscous, because they can
 9 produce finer particles of the unused liquid coating than
 10 do smooth discs at the same rotational speed.

11 In operation, the coating material 21 in liquid or
 12 slurry form is disposed in reservoir 20. If the coating
 13 material 21 is a wax, the wax is melted by heating. If a
 14 polymer coating material is used, it may be dissolved in
 15 a solvent, if necessary. The coating liquid may contain
 16 emulsified or suspended particles if they are desired in
 17 the final wall or coating on the core particle. The core
 18 material must be solid particles, granulated aggregates
 19 of fine particles or droplets of liquid which is more
 20 viscous than the liquid coating material 21. These
 21 particles or droplets 27 preferably, but not necessarily,
 22 should have a relatively narrow size distribution. When
 23 the droplets or particles are fed into the slurry of
 24 coating material 21, the stirrer 29 may be actuated by
 25 stirrer motor 30 to disperse the particles 27 in the

1 material 21. With the particles properly dispersed (and
 2 this may be a continuous process), the disc drive motor
 3 17 is actuated and set to the desired speed by speed
 4 control 19. This desired speed will depend primarily
 5 upon the size of the smaller excess coating particles to
 6 be produced as described below. Ball valve 33 is then
 7 actuated by means of actuator rod 39 to permit the
 8 suspension to flow onto the surface 13 of disc 11. Valve
 9 33 is opened slowly until the desired flow rate is
 10 achieved. The centrifugal force acting upon the
 11 suspension material as it hits the surface 13 causes the
 12 material to be thrown radially outward on the surface or
 13 grooves 24. This has the effect of dispersing the
 14 suspension into both particles 27 wetted with the coating
 15 liquid and smaller droplets of coating liquid which do
 16 not contain the core particles 27. The heating of the
 17 region surrounding disc 11 maintains the coating material
 18 in liquid state on surface 13. However, when the
 19 material is thrown from or falls from disc 11, the
 20 material falls through dry cooler air which causes the
 21 coating material to solidify by cooling or drying. The
 22 solidified small droplets of excess coating material and
 23 the core material coated with the solidified coating
 24 material fall to the bottom of the chamber during the

1 solidification process. Sieving, or other separation
 2 techniques, may be employed to separate the coated
 3 particles from the smaller particles of pure coating
 4 material. The smaller coating material pieces may then
 5 be recycled into the process by delivering such pieces
 6 into reservoir 20. The majority of the original
 7 suspended particles are coated discretely and similarly,
 8 a feature which is achieved by virtue of the fact that
 9 the original core material particles 27 are carefully
 10 dispersed in the coating material before the suspension
 11 is fed to the rotating disc. The coating thickness may
 12 be varied mainly by changing the viscosity of the coating
 13 liquid, but also by adjusting the feed rate of suspension
 14 to the disc, by varying the rotational speed of the disc,
 15 by varying the diameter of the disc or by varying the
 16 number of grooves or vanes.

17 It is possible to perform the method of the
 18 invention as a continuous process by feeding the coating
 19 liquid 21 and particles 27 into reservoir 20 on a
 20 continuous basis. An endless conveyor belt disposed at
 21 the floor of chamber 10 collects the particles and feeds
 22 them to a train of sieves which discriminate between
 23 coated particles and the smaller particles of pure
 24 coating material. The latter may be delivered directly
 25 to the reservoir 20 whereas the coated particles may be

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1 dispensed in any manner desired. Alternatively, all of
2 the particles may be pneumatically conveyed into a
3 cyclone, sieves or bag filter for separation of smaller
4 excess coating droplets to be recycled.

5 As previously noted, the process parameters are
6 specifically controlled, in a manner to be described, so
7 as to provide a separation of the liquid suspension by
8 means of the disc into coated particles (generally these
9 will be individually coated particles unless the process
10 is operated at low enough speed so that a small fraction
11 of the particles remain as doublets or triplets, or if
12 there is a wide size distribution of feed particles such
13 that the finer core particles are trapped in larger
14 particles) and droplets of excess coating liquid of
15 significantly smaller size than the coated particles.
16 The effect of the rotating disc on the suspension fed to
17 it is vividly illustrated in Figures 6 to 8. It will be
18 seen that the coating liquid 21 in the suspension is
19 gradually pulled away from the core particles 27, forming
20 a liquid film on the disc, as the suspension moves from
21 the center toward the periphery of the disc, with
22 progressive decrease in thickness of the liquid film or
23 sheet and finally separation of the excess liquid from
24 the particles 27, leaving a coating layer 27a on the
25 particles and dispersing the excess coating into a spray

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1 of small droplets 21a formed from the thin coating film.
2 Figures 6 and 7 show this effect for a disc with a smooth
3 upper surface, and Figure 8 shows the effect with a
4 grooved disc. The size of the atomized droplets of
5 excess coating bears little relation to the size of the
6 solid coated particles, but depends rather on the film
7 spreading and atomization characteristics of the liquid
8 coating alone. The core particles, by contrast, move by
9 a totally different mechanism, not spreading into a film
10 but simply being thrown through or along the film of
11 coating, issuing from the disc periphery with a small
12 amount of associated coating material.

13 Figure 12 shows a typical product in accordance
14 with the invention as it is sprayed or expelled from a
15 rotating surface. It will be evident that the product
16 consists of core particles 27 with a liquid coating layer
17 27a all generally of similar size, and droplets 21a of
18 excess unused coating material 21 which are of
19 significantly smaller size than the coated particles and
20 which have a size distribution typical of that expected
21 for simple atomization of the pure coating liquid. The
22 product shown in Figure 12 is in vivid contrast to
23 typical products of prior art processes which use a
24 rotary wheel or the like to provide dispersion of

1 suspended particles. Thus, Figures 9 to 11 show the
2 product of a typical prior art process (spray drying) in
3 which particles are imbedded in droplets of a liquid
4 containing a solvent, by forming a slurry of the
5 particles in the liquid and forming droplets of the
6 slurry by feeding the slurry to a rotary wheel or the
7 like. As shown in Figure 9, the product as it leaves the
8 wheel contains particles 127 with a liquid coating 127a
9 and separated droplets 121 of excess coating material.
10 However, it will be evident that there is no sharp size
11 discrimination, as in products of the present invention,
12 between the coated particles (which are usually coated in
13 clusters, but some of which will be coated singly) and
14 the droplets of excess coating material. Thus, there are
15 a significant number of droplets 121 which are comparable
16 in size to the coated particles, in contrast to products
17 of the present invention where the droplets predominantly
18 are significantly smaller than the coated particles and
19 most large particles are coated discretely. Accordingly,
20 subsequent removal of excess droplets of coating
21 material, by sieving, centrifuging or the like, is
22 facilitated with products according to the invention
23 compared with the products of the prior art processes.
24 Figure 10 shows the prior art product of Figure 9 after
25 evaporation of the solvent, and Figure 11 shows the
26 product after removal of the smaller excess coating

1 droplets, for example by sieving, illustrating the rather
2 high percentage of unused coating material (in the larger
3 droplets thereof) which has not been removed from the
4 coated product. It is essentially impossible by this
5 prior art process to produce product particles with core
6 loadings above 50%, to remove excess coating, and to have
7 high particle-to-particle uniformity. Looked at in the
8 alternative, the invention provides a product comprising
9 relatively large, predominantly individually coated
10 particles and uncoated droplets predominantly of
11 significantly smaller size than the coated particles,
12 whereas prior art products are predominantly a mixture of
13 individual mass components of coated particles and
14 uncoated droplets of generally similar dimensions wherein
15 the core particles themselves are relatively small
16 compared to the final particles.

17 In order to obtain a product wherein there is a
18 sharp size discrimination between the coated particles
19 and the droplets of excess coating liquid, the process
20 parameters in accordance with the invention are
21 controlled in a particular manner. More particularly, in
22 accordance with the invention, the rotational speed of
23 the disc or the like is related to the average mean size
24 required for the droplets 21a (as will be described in
25 more detail below) rather than relating the rotational

1 speed of the disc or the like to the average size
2 required for the coated particles. By contrast, in the
3 prior art processes, the speed of the rotary wheel or the
4 like is related to the size required for the formed
5 droplets irrespective of whether they contain imbedded
6 core particles or not. Thus, in the present invention,
7 the disc or the like is run at surprisingly higher speeds
8 than in the prior art for producing coated core particles
9 of similar size to the particles of the prior art.

10 As noted above, in carrying out the invention, the
11 speed of rotation for the disc is related to the required
12 mean droplet size for the excess coating material rather
13 than to the required size of coated particles and in this
14 process, changes in the disc speed have significantly
15 less effect on the thickness of coating on the large core
16 particles. It is well known in industrial spray drying
17 and spray chilling techniques using rotary disc-type
18 atomizers that there are mathematical correlations
19 between the disc speed and the average droplet size
20 expelled from the disc, see for example pages 179-184 of
21 "Spray Drying Handbook" by K. Masters, 3rd Edition, John
22 Wiley & Sons, New York (1979), and which is specifically
23 incorporated herein by reference. These correlations may
24 be used to provide an estimate of required disc speed for
25 the present invention, (possibly incorporating a

1 viscosity correction factor in the correlations to
2 compensate for the effect of hot air flow as in Figures 3
3 and 4) once the desired average droplet size for the
4 excess coating liquid has been established. This desired
5 average droplet size may be established from known
6 droplet size distribution estimates, for example, using
7 log-probability graphs (also discussed in the above
8 reference) and relating the estimated droplet size
9 distribution to the acceptable contamination percentage
10 in the final product, i.e., the percentage of acceptable
11 excess coating droplets of a size making them impractical
12 to separate from the coated particles. Again, it should
13 be stressed that while techniques are known for
14 estimating disc speed in relation to a required droplet
15 size and for estimating droplet size distributions, these
16 have not previously been utilized in the present manner
17 whereby, in a particle coating process, disc speed is
18 related to a predetermined size required for the droplets
19 of excess coating liquid rather than being related to the
20 size required for the coated product particles
21 themselves. Also, it is understood that the correlations
22 referred to above for determining the required disc speed
23 may be used for estimation purposes, and in practice, it
24 may be desirable somewhat to adjust the disc speed
25 empirically.

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1 To illustrate the significant difference in
2 rotational speeds used in processes according to the
3 invention compared with prior art processes, the various
4 parameters used in a typical prior art spray cooling-type
5 particle embedding process may be compared with the
6 parameters used in a process in accordance with the
7 invention for coating like particles with a like liquid
8 coating. Thus, for example, if it is required to coat
9 ion-exchange resin beads having a sieve fraction 53-106
10 microns with a wall material of 9/1 paraffin wax/Elvax
11 420 (Dupont ethylene-vinyl acetate copolymer, melt index
12 150) in a spray cooling procedure in accordance with a
13 typical prior art process, the rotational speed of an
14 8-inch diameter (0.2 meter) disc type atomizer typically
15 would be set at about 3,000 r.p.m. for a feed rate of 4.5
16 kg/hr of slurry containing 2/1 wt ratio of coating to
17 core particles, with a coating viscosity of 50 centipoise
18 to give an average fluid drop in the atomized slurry
19 close to the size just containing the largest core
20 particle. For the largest single core particle at 70%
21 loading in the final microcapsule, this droplet size
22 would be 120 microns and setting the rotational speed at
23 3,000 r.p.m. would give an average droplet size of about
24 118 microns from the correlation noted above. However,
25 this will be the average particle size in the atomized
26 slurry both for particles containing the core material

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1 and also for droplets of the excess pure coating
2 material. A product obtained from this prior art process
3 at these conditions showed a substantial overlap in
4 particle size distribution of the coated particles and
5 the unused coating droplets so that it was not practical
6 to effect a separation based on size.

7 By contrast, in a process in accordance with the
8 present invention, if it is estimated that the smallest
9 microencapsulated product including the above beads will
10 have a diameter of 67 microns at approximately 50%
11 loading of the 53-micron core particle, the rotational
12 speed of a disc may be set for example to run at 8,000
13 r.p.m. to give an average particle diameter for unused
14 coating droplets of about 40 microns. To estimate the
15 amount of unused coating droplets which might be in the
16 microencapsulated product, a log-probability graph, as
17 described above may be used and results in a
18 contamination rate of about 10% for a product sieved at
19 67 microns. A run was also made under these conditions,
20 but using an 8-inch vaned disc giving somewhat smaller
21 droplets of excess coating. After sieving at 53 microns,
22 the contamination, measured by counting coated particles
23 and remaining pure coating particles, was approximately
24 7%.

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1 The correlation referred to above with the
 2 viscosity term modified to mirror the effect of hot air
 3 moving over the surface is:
 4

$$\bar{x} = \frac{(1.4 \times 10^{-4})(N_L)^{0.24} (V)^{0.1}}{(Nd) \frac{0.83}{(\pi d)} \frac{0.12}{15}}$$

where \bar{x} = Average droplet diameter (microns)

N_L = Liquid feed rate (kg/hr)

N = Rotational speed (RPM)

d = Disk diameter (meters)

V = Viscosity (centipoise)

πd = Wetted periphery (meters). Use πh for disks with
 n vanes or grooves h meters high.

5 As noted above, one of the parameters which may
 6 be adjusted to vary the thickness of the coating material
 7 on the final coated particle is the viscosity of the
 8 coating liquid. In this regard, when wax is employed as
 9 a coating material, the viscosity can be readily lowered

1 to thereby provide thinner coating walls on the final
 2 coated particle, by adding solvents to the molten coating
 3 material 21. When the inclusion of a polymeric material,
 4 e.g., polyethylene in the coating is desirable the
 5 viscosity can be lowered significantly through addition
 6 of compatible materials of substantially lower viscosity,
 7 e.g., waxes. In general, the solid particles 27 of core
 8 material should be insoluble in the liquid coating
 9 material 21; however, if the contact time between the
 10 core material 27 and the coating material 21 is
 11 sufficiently short before the coating material
 12 solidifies, solids may be coated before they dissolve.
 13 In this way, water soluble or water sensitive solids may
 14 be coated by an aqueous solution. Likewise, droplets of
 15 viscous liquids (i.e., of significantly greater viscosity
 16 than the coating material 21) may also be coated.

17 In some applications the materials may be selected
 18 such that the solid core material 27 reacts with the
 19 coating liquid 21 so as to form an initial solid wall at
 20 their juncture before the coating material 21 is
 21 solidified during the process. Thus, the core material
 22 27 might contain a polyfunctional acid chloride, or
 23 isocyanate, and the liquid 21 might contain a polyamine
 24 or polyol. This technique is also useful for coating a
 25 liquid since the initial wall or shell formed by the

1 chemical reaction between the two materials prevents
 2 absorption or dispersal of the core material into the
 3 coating material or aggregation of the core particles
 4 before the coating material solidifies.

5 Coatings of slurries may be formulated by
 6 suspending the solids desired in the coating liquid prior
 7 to, or simultaneously with, the suspension of the core
 8 particles. Suspended solids in the coating may be
 9 soluble in the coating if their contact time with the
 10 coating is insufficient to permit dissolution.

11 Liquids may also be coated by dispersing them to
 12 form a suspension or emulsion in the coating liquid. The
 13 core liquid should have a viscosity higher than that of
 14 the coating liquid so that the spread of liquid and
 15 subsequent atomization into small drops occurs primarily
 16 in the coating liquid. Liquid core materials may also be
 17 coated after they are absorbed onto or into solids.

18 It is also possible to catch the coated particles
 19 on a layer of powder or in a hardening or extraction bath
 20 in which additional solvent is removed by extraction or
 21 in which a chemical hardening reaction occurs. An
 22 example of the latter would be the formation of

1 gelatin-coated particles which are caught in a bath
 2 containing glutaraldehyde which hardens the wall or
 3 coating material and greatly decreases the permeability
 4 of the wall.

5 It is possible to use the invention to produce
 6 walls of polymers which are insoluble in all or nearly
 7 all solvents when the polymers are available in the form
 8 of aqueous latex suspensions. Examples are acrylics,
 9 rubber, synthetic rubber, polyvinylidene chloride, etc.
 10 The solid or droplet core particles are suspended in the
 11 latex and the suspension fed to the rotating element
 12 according to the present invention. Moist air must be
 13 blown over the disc surface or other means provided to
 14 prevent the latex from drying and coagulating on the
 15 disc. After the coated particles and smaller excess pure
 16 latex particles leave the disc they are dried, e.g., by
 17 falling through a chamber through which hot unsaturated
 18 air or gas is passing. As water is removed from the
 19 latex, the polymer particles coagulate into an insoluble
 20 film. When dry the film coating is a tight barrier only
 21 affected by solvents for the polymer.

22 Another embodiment of the present invention is
 23 illustrated in Fig. 2 to which reference is now made. A
 24 rotating disc 11 with a grooved top surface 13 and its

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1 drive motor 17 are similar to like components illustrated
 2 in the embodiment of the Fig. 1. Infrared heat lamps 40
 3 are employed to heat the space above disc 11 and a
 4 stirrer motor 30, having its speed controlled by a VARIAC
 5 41, stirs the coating and core materials to provide the
 6 necessary suspension. A heated funnel 45 is selectively
 7 raised and lowered along three threaded vertical support
 8 rods 49, only two of the support rods being illustrated
 9 in Fig. 2. The stirrer 50 is disposed within funnel 45
 10 and is rotated by means of drive shaft 47 connected to
 11 stirrer motor 30. The distal end of shaft 47 is in the
 12 form of a plug 51 which, depending upon the height of the
 13 funnel 45 on support rods 49, may project through the
 14 lower funnel opening and thereby close off outflow from
 15 the funnel to the disc 11. This embodiment eliminates
 16 the ball valve and provides flow control by means of the
 17 raising and lowering of the funnel on shafts 49, or by
 18 raising and lowering the motor. Many more feed schemes
 19 will be apparent to those skilled in the art.

20 Another embodiment of the present invention is
 21 illustrated in Fig. 3 to which detailed reference is now
 22 made. A rotating disc 55 having a smooth flat upper
 23 surface 57 is disposed horizontally between two
 24 horizontal walls 59 and 60. A funnel 61 contains a
 25 stirrer 63 placed to suspend solid particles in liquid

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1 coating material which is added simultaneously to the
 2 stirred funnel. The lower end of funnel 61 extends
 3 through a suitably provided opening 65 in upper wall 59
 4 so that the bottom opening of funnel 61 is disposed to
 5 permit the funnel contents to fall on the disc surface 57
 6 in alignment with the rotation axis of the disc. A
 7 distribution cone 67 diverges downwardly and is disposed
 8 substantially concentrically about the funnel stem so as
 9 to prevent splashing of the slurry material delivered
 10 from the funnel to the disc surface. Hot air is
 11 channeled to the region between plates 59 and 60, both
 12 above the disc 55 and below it, by means of suitable hot
 13 air conduits 69 which communicate with suitable openings
 14 in plates 59 and 60. The temperature of the air
 15 delivered through conduits 69 is sufficient to maintain
 16 the coating material in molten form when it is located in
 17 the region between plates 59 and 60. It is apparent that
 18 the plates aiding in controlling air flow need not be
 19 parallel. For example, higher hot air velocity at the
 20 edge of the rotating disc can be achieved with the gap
 21 between plate and rotating disc decreasing as the radius
 22 increases. It is also apparent that the plates may
 23 rotate in common with the disc.

24 In the Embodiment of Fig. 3, the funnel 61 serves
 25 as the vessel in which the solid particles or liquid
 26 droplets of core material are dispersed in the coating

1 liquid. In addition, the feed rate of the resulting
2 suspension from the funnel onto disc surface 57 is
3 controlled by the level of suspension maintained in the
4 funnel rather than by a funnel outlet valve mechanism.

5 The embodiment of Fig. 4 is similar in many
6 respects to the embodiment of Fig. 3 except for the
7 suspension feeding mechanism and for the fact that the
8 disc is tilted at an angle, e.g., forty-five degrees,
9 relative to horizontal. The suspension of coating and
10 core materials is disposed in a vessel 70 having a
11 stirrer 71 therein. A lower corner portion of the vessel
12 70 is selectively openable to permit controlled feeding
13 of the suspension material onto the top surface 57 of
14 disc 55. Fig. 4 is intended to illustrate that the disc
15 can be oriented at substantially any desired angle and
16 need not be horizontal as shown in Figs. 1 - 3.

17 The embodiment of Fig. 5 diagrammatically
18 illustrates the use of a generally conical mesh screen 77
19 disposed above the top surface of a disc 75 so as to
20 converge to a location between the disc and the lower end
21 of a funnel 73. The funnel delivers the suspension
22 material toward the disc 75 in the manner described above
23 in relation to the embodiments of Figs. 1 - 3. However,
24 the mesh screen 77, which rotates with disc 75, is

1 provided to aid in controlling the average coating
2 thickness by draining away part of the coating material
3 through the screen. Further forms of rotary discs 90,
4 92, 94 which may be used for the invention are shown in
5 Figs. 13 to 15. In addition, multi-tier rotating discs,
6 vaned wheels, grooved discs and radial tubes can be
7 employed.

8 The invention as described hereinabove is suitable
9 for coating particles of substantially any shape;
10 however, the most uniform coating is obtained with
11 spherical particles. Particle size may generally vary in
12 the range from 10 micrometers to 10 millimeters, although
13 special designs or conditions will permit the use of
14 particles outside this range. Nearly spherical
15 particles may be readily formed by techniques well known
16 in the prior art, such as spray drying or prilling, by
17 extrusion or compression in molds, or by agglomeration of
18 fine powders in rotating drums using a liquid phase
19 binder and/or heat. It is also known that compact
20 crystals approaching a spherical shape may be obtained by
21 attrition during crystallization.

22 The preferred coating material for minimum process
23 cost should be liquid at coating temperature and should
24 solidify when cooled, without requiring either

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1 evaporation of a solvent or a chemical reaction. The
2 viscosity of the coating material may range from 0.5 to
3 100,000 centipoises, with preferred viscosities between
4 1-5,000 centipoises. Preferred coating liquids are
5 various mixtures of polyolefins, ethylene-vinyl acetate
6 copolymer and waxes. A typical coating liquid
7 composition is 50 percent by weight polyethylene of
8 density 0.92, melt index 250, and 50 percent paraffin wax
9 having a melting point of 60° C. It is preferable that
10 the core material is insoluble in the coating liquid at
11 coating temperature, although soluble cores can be coated
12 if the contact time with the coating before spraying and
13 solidification is sufficiently short to prevent
14 dissolution.

15 During a typical operation, as noted above, the
16 particles to be coated may constitute up to 45 percent by
17 volume of the overall suspension slurry, although in
18 general the percent by volume will be in the 20-35%
19 range. The temperature surrounding the top surface of
20 the disc must be above the melting point of the coating
21 material. Typically, this may be between 60° and 90° C
22 for pure waxes and 120° to 160° C for polymer/wax
23 mixtures.

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1 The rotational speed of the disc is chosen so that
2 the excess coating material produces much smaller spheres
3 than the coated particles. If the disc were used simply
4 as an atomizer for the coating liquid it is these small
5 spheres which would be produced. Since the excess liquid
6 wall material forms smaller droplets, the aerodynamic
7 drag force per unit mass is much higher than that for the
8 larger coated particles. Hence, as these smaller
9 droplets solidify they are slowed down much more quickly
10 by the drag force as they move away from the spinning
11 disc. These droplets, therefore, fall much closer to the
12 spinning disc. A receiver may be placed near the disc to
13 catch these small unused coating particles for recycling
14 back to the coating reservoir. Alternatively, the unused
15 coating particles may be caught in the inner portion of
16 the bottom cone for sieving and recycling.

17 When the ring of unused coating particles partly
18 overlaps the ring of coated particles, the particles
19 cannot be totally separated by sieving. When this
20 occurs, an increase in rotational speed of the disc
21 causes a separation of the rings, by throwing the coated
22 particles farther and decreasing the size of the unused
23 coating particles so that they fall closer to the disc.
24 When the product particles are less than 100 microns in
25 diameter, both the product and the smaller excess coating

1 particles fall within a few feet of the disc and are both
 2 strongly affected by the air blowing outward along the
 3 radius of the disc. Hence they do not separate cleanly
 4 into distinct rings. However, they are easily separated
 5 by sieving, centrifugal force, etc.

6 For particles in the range of 0.5 millimeter
 7 diameter and a density of 1.2, a rotational speed of
 8 1,000 - 1,500 rpm for a disc of 8 inches diameter
 9 provides good spatial separation of the fine excess wax
 10 particles from the much larger coated particles so that
 11 the excess wax particles may be collected separately and
 12 may not require a separate sieving operation.

13 The particles to be coated may be mixed with the
 14 melted coating material immediately before the resulting
 15 suspension is fed to the disc. Feeding rates for a disc
 16 having an 8 inch diameter are preferably on the order of
 17 100 milliliters to 5 liters per minute but can cover the
 18 range of 10ml/min to 100 liters/min. For coating
 19 materials with melting points substantially above room
 20 temperature (e.g., above 50° C), the coated particles
 21 solidify rapidly after leaving the disc surface and may
 22 be collected immediately. If a solution is used as the
 23 coating, then the solvent has to be evaporated before
 24 essentially dry particles can be collected.

1 The embodiments described above include a disc
 2 having a grooved surface, a disc having a flat smooth
 3 surface, cupped or cone-shaped surface, and angled
 4 screens or perforated plates disposed above a reservoir
 5 (rotating or non-rotating). It is also possible to
 6 provide a vaned disc whereby the disc comprises a
 7 plurality of angularly spaced vanes with gaps
 8 therebetween. Virtually any rotating device which can be
 9 used for atomization may be used in the present
 10 application, as long as the slurry does not have to pass
 11 through a fine orifice where plugging may occur.

12 Other alternatives are an inverted cone made from
 13 stainless steel screen and a vaned disc in which the
 14 vanes are placed at an angle to the disc diameter.

15 In employing the invention, we have successfully
 16 coated the following substances: phosphors (12-60
 17 micrometers), potassium chloride angular particles
 18 (25-300 micrometers), potassium chloride (approximately
 19 spherical particles 500-860, 250-500, 120-250
 20 micrometers), water thickened with carboxymethyl
 21 cellulose, sucrose crystals (1-1.5 millimeters), sucrose
 22 spheres (1.4-2 millimeters), aspirin powder (held
 23 together with carboxymethyl cellulose solution).

EXAMPLE I

1 acetaminophen (180-320 micrometer spheres), etc..
 2 Coating liquids which we have employed include pure wax,
 3 wax with solvents (e.g., paraffin wax 20 percent, Polywax
 4 500 30 percent, 1,1,2, trichloroethane 50 percent), wax
 5 mixtures (Polywax 500 16 percent, ethylene vinylacetate
 6 copolymer (Elvax 420, 18% vinyl acetate, Du Pont de
 7 Nemours, Inc.) 24 percent and paraffin wax 60 percent;
 8 or paraffin wax 17 percent, Polywax 500 33 percent and
 9 Elvax 420 50 percent), polyethylene wax, wax and low
 10 density polyethylene (paraffin 50 percent and
 11 polyethylene 50 percent), Woods metal (50 percent
 12 Bismuth, 25 percent Lead, 12.5 percent Cadmium and 12.5
 13 percent Tin), cellulosic polymer dissolved in a solvent,
 14 and solutions of mixtures of waxes, polyethylene and
 15 ethylene-vinyl acetate copolymer in aromatic and
 16 aliphatic hydrocarbons. Coating materials have also been
 17 used in the form of slurries containing up to 37 mass
 18 percent of suspended insoluble solids, both smaller than
 19 and greater than the average final wall thickness.

20 The present invention is further illustrated by
 21 the following examples:

2 In this example, nearly spherical particles of
 3 potassium chloride were used, the particles being of a
 4 20-32 mesh (500-863 micrometers) fraction obtained by
 5 sieving. The apparatus was substantially that
 6 illustrated in Fig. 1 with the top surface of disc 11
 7 smooth rather than grooved. The outlet opening 37 for
 8 the ball valve was disposed approximately 1/8 inch above
 9 the surface 13 of the disc. The entire reservoir was
 10 heated by electrical tape and was equipped with a
 11 thermocouple. The disc was inclined at about 45 degrees
 12 from horizontal (as in the Fig. 4 embodiment) to increase
 13 the path of the upward-directed particles in the air so
 14 as to allow them to solidify before encountering a solid
 15 surface. (The downward-directed particles were not
 16 collected). The disc assembly was equipped with three
 17 heat guns above the disc and two below the disc in
 18 addition to the two heat lamps.

19 Thirty-eight grams of paraffin wax (Fisher P-22),
 20 38 grams of Polywax-500 (made by the Bareco Division of
 21 Petrolite Inc.), and 24 grams of Elvax 420 (DuPont) were
 22 melted and mixed in a beaker. The molten wax and 38
 23 grams of potassium chloride particles were mixed in the
 24 heated mixing reservoir. With all the heat guns on, the

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1 disc was then turned on to rotate at 700 rpm. The valve
2 was opened to allow the suspension to flow onto the
3 center of the disc from which it was dispersed. Coated
4 potassium chloride was thrown in an upward trajectory
5 (because of the angle of the disc with respect to
6 horizontal) landing at floor level roughly six feet away
7 from the disc. The smaller pure wax particles followed a
8 path much closer to the disc, separated by one or two
9 feet from the coated potassium chloride particles.

10 The large particles were separated into three
11 fractions by sieving. Twenty-eight percent were greater
12 than 860 micrometers in diameter; 68% were between 590
13 and 860 micrometers in diameter; and 4% were less than
14 590 micrometers in diameter. The small wax particles
15 immediately around the disc were not recovered.

16 The mean diameter measured for a small number of
17 uncoated particles ($n=15$) was 521 ± 44 micrometers. The
18 coated particles had a mean diameter of 759 plus or minus
19 74 micrometers ($N = 15$). Therefore, the mean wall
20 thickness based on these measurements was 119
21 micrometers.

22 In the fraction having a diameter greater than 860
23 micrometers, all the particles sank in a liquid of
24 density approximately 10% greater than that of the wax

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1 (i.e., diethyl succinate having a density of 1.047 grams
2 per cubic centimeter). This indicates that all these
3 particles contained potassium chloride. In the particles
4 having diameters in the range of 590-860 micrometers,
5 three particles out of twenty randomly chosen particles
6 floated, indicating that they were pure wax. (The
7 fraction of pure wax particles in this size range could
8 be decreased by higher disc speed or lower coating
9 viscosity). Water extraction showed that the fraction
10 having diameters greater than 860 micrometers contained
11 54.7% potassium chloride, and 45.3% wax; the fraction
12 having 590-860 micrometer diameter contained 65%
13 potassium chloride and 35% wax.

14 Whereas the free potassium chloride dissolved
15 within seconds when placed in water, less than 3% of the
16 coated potassium chloride (of either size fraction)
17 dissolved in ten minutes. Only 16.2% dissolved in 70
18 minutes from the 590-860 micrometer fraction, and 30.9%
19 dissolved in 70 minutes from the fraction having
20 diameters greater than 860 micrometers. In 266 minutes,
21 39% dissolved from the fraction in the range of 590-860
22 micrometer diameter, and 62% from the fraction having
23 diameters in the range greater than 860 micrometers.
24 This indicates that the soluble potassium chloride
25 particles were well coated.

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1 In this example (I) the potassium chloride was
2 well coated by the waxy polymer coating. This is
3 difficult by methods such as fluid-bed coating because
4 the waxy droplets do not wet the potassium chloride
5 surface well. Hence, the coating spreads poorly over the
6 surface. In the present invention, the particles start
7 by being totally immersed in the coating, and the process
8 is so rapid that the coating does not have sufficient
9 time to uncover the surface before solidifying.

10 EXAMPLE II

11 Non-pareil sugar spheres ranging from 1.2 to 2
12 millimeters in diameter were encapsulated in wax having
13 the following composition: Gulfwax (household paraffin
14 wax) 38 grams; Polywax 500 (Bareco) 38 grams; and Elvax
15 420 (DuPont) 24 grams. While the wax was stirred at 104°
16 C in the mixing vessel, 40 grams of non-pareil spheres
17 were added, mixed well and the dispersion was poured on
18 to the disc, which was spinning at 1140 rpm. The
19 resulting wax coating on the coated non-pareils ranged
20 from 17 to 25% by weight when measured by extraction.
21 Uncoated non-pareil spheres released 73.6% of their
22 contents in ten minutes and 91% in thirty minutes.

1 Coated spheres did not release a detectable amount in ten
2 minutes (i.e., less than 1%). After thirty minutes, 1.1%
3 was released, and after one hour 2.6% was released.
4 Hence, the sugar was well coated.

5 EXAMPLE III

6 Twenty grams of cellulose acetate butyrate
7 (Eastman CAB 381-2) were dissolved in a mixture of 100
8 milliliters dichloromethane and 10 milliliters acetone
9 and placed in reservoir 20. Red sugar crystals having a
10 total weight of 28 grams and passing through a 500-micron
11 sieve but retained by a 250-micron sieve were mixed with
12 the CAB solution and the suspension fed to the disc
13 rotating at 1170 rpm without heating. The red particles
14 were well separated from the smaller, uncolored polymer
15 droplets during the coating operation. The fraction of
16 the coated product passing a 1 millimeter sieve but
17 retained by 860 micrometer openings (coated particles
18 agglomerated on the receiving surface due to inability to
19 evaporate all the solvent in the laboratory air) were 68%
20 sugar and 32% cellulose acetate butyrate coating. When
21 placed in water, 33% of the sugar dissolved in ten
22 minutes, and 65% in 90 minutes.

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EXAMPLE IV.

1 In order to coat with polymeric compositions of
 2 higher melt viscosity (e.g., polyethylene), it is
 3 necessary to control the air temperature adjacent to the
 4 rotating disc. This was achieved to a greater extent
 5 using the embodiments of Figs. 3 and 4 wherein the cover
 6 plates 59 and 60 were employed. Hot air (for example,
 7 from heat guns) is conducted directly through conduits 59
 8 toward the disc.

10 100 grams of polyethylene (melt index = 250) was
 11 melted in a beaker. 34 grams of spherical granules of
 12 slightly water-soluble organic acid, having a number mean
 13 diameter of 0.740 millimeters, was mixed with the molten
 14 polyethylene. The temperature of the mixture was 154°
 15 C. This was delivered to the disc which was rotating at
 16 1140 rpm. The temperature of the plates facing the disc
 17 ranged from 130° to 170° C at different points. The
 18 viscous suspension was fed to the plate over a period of
 19 five minutes. 46 grams of material which did not contact
 20 a wall were recovered and were distributed as follows:

1	Diameter (Micrometers)	% of total	Content
2	500	7.8	Polyethylene only
3	500-590	0.9	Polyethylene only
4	590-860	7.3	coated organic acid
5	860-1000	14.5	coated organic acid
6	1000-1180	9.1	coated organic acid
7	1180 particulate	3.7	several spheres
8	non particulate	56.7	"Caffy" and "spider webs", polyethylene
9			containing no organic
10			acid.
11			

12 (The non-particulate material is not observed at lower
 13 coating viscosity, but higher temperature could not be
 14 employed in this example to lower the viscosity owing to
 15 the thermal instability of the core particles).

16 For comparison, the particle size distribution of the
 17 uncoated organic acid spheres was as follows:

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1	Diameter (micrometers)	wt %
2	500	0.4
3	500-590	1.2
4	500-860	79.2
5	860-1000	19.0
6	1000	0.3
7	The particles in size fraction 590 to 1000 micrometers contained 49% organic acid. When placed in deionized water 2.4% of the organic acid was released in 16 hours, 7.1% in 72 hours. In the uncoated control runs, the organic acid dissolved entirely in approximately 30 minutes.	

EXAMPLE V

14 400 gm Woods metal, (obtained from Federated Metal Corp. of Newark, N.J.) was melted in a beaker. 50 gm of nearly spherical KCl, passing a sieve with 860 micron openings but being retained by a 500 micron sieve, was heated to 85° C in an oven. An 8-inch disc with twenty-four grooves 1/8 inch wide and 1/16 inch deep, held at 60° C and an inclination of 28 degrees with the horizontal, was rotated at 6,300 rpm. A suspension of KCl particles in the liquid Woods metal was formed and poured onto the disc.

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1 The distribution of particle sizes was as follows:

2	Diameter (micrometers)	Wt/(gm)	Content
3	Below 500	26.3	metal dust
4	500-590	21.8	spheres
5	500-860	10.0	spheres and flat pieces
7	Above 860	37.1	agglomerates

8 The spheres were covered with the metal as determined by visual observation, but the potassium chloride dissolved readily, indicating that the coating was porous. Under the microscope the coating was seen to consist of many small metal crystals, giving the likelihood of leakage at crystal boundaries.

EXAMPLE VI

15 50 gm Polyethylene USI (density = 0.927, melt index = 250) was dissolved in 50 gm Gulfwax Paraffin at 150°C. The flat, smooth 8-inch diameter disc was held at 130°C

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1 and rotated at 1,800 rpm. 50 gm of nearly spherical
 2 acetaminophen particles, 177 - 250 micrometers was mixed
 3 with the polymer/wax solution. The 177 - 300 micrometers
 4 product fraction contained mostly coated single
 5 particles.

EXAMPLE VII

7 The cone-screen embodiment of Fig. 5 was employed
 8 in coating nearly spherical KCl. The percent core
 9 material relative to total particle (i.e., payload)
 10 increased in the product from a run made under the same
 11 conditions using a flat disc. This demonstrates that the
 12 porous cone represents another means to control wall
 13 thickness by increasing the amount of coating liquid
 14 drained away from the core particles, and also decreases
 15 the fraction of excess coating liquid atomized from the
 16 edge of the rotating device. There is, however, a
 17 decrease in the number of discretely coated particles.

18 Coating composition was 38% by weight paraffin wax
 19 (Gulf), 38% by weight Polywax 500, Bareco, and 24% Elvax
 20 420 (Dupont). Original particle size range was 0.50 to

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1 86 mm. The slurry was fed to the disc or rotor at 116
 2 degrees centigrade, with the air between the plates kept
 3 at 129-133°C.

% Payload

	500-590 micrometers	590-850 micrometers
6 Flat Disk	75.8	57.3
7 Cone Screen	88	82.8

8 For the smooth disc, operated at the same
 9 conditions the size distributions of uncoated core
 10 particles, coated particles and atomized excess coating
 11 were as follows:

	Diameter (micrometers)	Weight (gm)	%
12 Uncoated KCl			
13	Smaller than 420	.418	2.5
14	420-500	2.354	14.0
15	500-590	13.187	78.6
16	590-860	0.654	3.9
17	Larger than 860	0.172	1.0
18	Total	16.785	100.0

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1 Product (in two rings around rotating device):

2 Coated KCL Particles (Outer Ring)

3 <u>Diameter (micrometers)</u>	4 <u>Weight (gm)</u>	5 <u>%</u>
6 Smaller than 500	.3	1.8
7 500-590	.6	3.6
8 590-860	12.1	73.4
9 860-1.00	2.6	15.8
10 1.00-1.18	0.5	3.0
11 Greater than 1.18	0.4	2.4
Total	16.5	100.00

12 Atomized Excess Coating (Inner Ring)

13 <u>Diameter (micrometers)</u>	14 <u>Weight (gm)</u>	15 <u>%</u>
16 Smaller than 149	1.0	5.5
17 149-177	0.9	5.0
18 177-250	1.5	8.3
19 250-297	3.3	18.3
20 297-420	7.3	40.6
21 420-500	1.3	7.2
22 Greater than 500	2.7	15.1
Total	18.0	100.00

1 There is only a small overlap in the size
 2 distribution of the large coated KCL particles (mostly
 3 single coated particles) and the small droplets, which
 4 consist mostly of atomized pure coating material. Since
 5 solid KCL is more dense, nearly all coated KCL particles
 6 would be in the outer circle. If the disc is operated at
 7 higher rotational speed or if the viscosity of the
 8 coating is decreased, the diameter of the atomized
 9 droplets in the inner ring decreases. The diameter of
 10 the ring containing the large coated particles will
 11 increase if rotational speed is increased, or will
 12 decrease slightly if speed is kept the same but viscosity
 13 is decreased, because they have a thinner coating.

14 We have described an improved method and apparatus
 15 for coating or microencapsulating solid particles or
 16 viscous liquid droplets applicable to a wide range of
 17 sizes. The coating technique works well for coating
 18 solids in the 20-300 micrometer range where prior art
 19 methods of spraying the coating onto fluidized particles
 20 work poorly or not at all. In general the method is less
 21 expensive than prior art processes because it is very
 22 rapid and requires less energy and process control.
 23 Contact time between the coating material and the core
 24 material can be maintained extremely short. In addition,
 25 the particles need only be handled once in the apparatus
 26 as opposed to many passages through the spray region of
 27 the spray coating methods.

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1 The present invention is also useful in place of a
2 variety of other processes for forming microcapsules.
3 For example, the method of the present invention obviates
4 the need for careful control and timed changes in
5 conditions required in many cases of coacervation and
6 solvent evaporation microencapsulation processes. The
7 present method avoids the difficulties of microcapsule
8 agglomeration, a frequent problem in these processes.

9 The method of the present invention is also useful
10 with dispersed liquid core droplets, made more viscous
11 than the coating liquid to limit the spreading and
12 atomization phenomena to the less viscous coating
13 material. In this manner, the process of the present
14 invention may be employed to form microcapsules similar
15 to those formed by the annular-jet method.

16 Having described several embodiments of the new
17 and improved method and apparatus for coating or
18 microencapsulating solid particles or viscous liquid
19 droplets in accordance with the present invention, it is
20 believed that other modifications, variations and changes
21 will be suggested to those skilled in the art in view of

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1 the foregoing description. It is therefore to be
2 understood that all such variations, modifications and
3 changes are believed to fall within the scope of the
4 invention as defined in the appended claims.

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1 WHAT IS CLAIMED IS:

2 Claim 1. A method of coating or encapsulating
3 individual mass components of core material having the
4 form of solid particles, aggregates formed by granulation
5 or liquid droplets with a coating of material that is
6 less viscous than the core material and solid at normal
7 room temperatures but liquid at elevated coating
8 temperatures, or in the form of a solution during the
9 coating process, said method comprising the steps of:
10 distributing said individual mass components of
11 core material throughout the liquid coating material to
12 form a suspension;
13 feeding the suspension onto a rotating surface
14 which centrifugally separates and disperses the
15 suspension into (1) droplets of pure coating material and
16 (2) individual components of said core material coated
17 with said coating material;
18 cooling the coated individual mass components or
19 removing solvent therefrom to solidify the coating
20 material;
21 and controlling the process so as to produce a
22 predominance of the droplets of excess liquid coating as
23 droplets of a predetermined size smaller than the size of
24 the coated individual mass components.

1 Claim 2. The method according to Claim 1 wherein
2 the step of controlling the process includes relating the
3 speed of rotation of the surface to said predetermined
4 size of the droplets.
5 Claim 3. The method according to Claim 1 further
6 comprising the step of separating said coated individual
7 mass components from the droplets of pure coating
8 material.
9 Claim 4. The method according to Claim 3 wherein
10 the step of separating includes sieving or use of
11 centrifugal force to separate the relatively large coated
12 individual mass components from the relatively small
13 droplets of coating material.

14 Claim 5. The method according to claim 3 wherein
15 the step of separating includes rotating said rotating
16 surface at sufficiently high speed such that the droplets
17 of pure coating material are significantly smaller than
18 the coated individual mass components and therefore fall
19 from said rotating surface at a location radially inward
20 from the separated coated individual mass components.

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1 Claim 6. The method according to Claim 1 wherein
 2 the step of cooling or removing solvent includes passing
 3 the coated mass components through ambient air or gas,
 4 heated or unheated, by centrifugally hurling the
 5 components from said rotating surface.

6 Claim 7. The method according to Claim 1 further
 7 comprising the step of heating the region at said
 8 rotating surface to maintain the coating material in
 9 liquid form at said rotating surface.

10 Claim 8. The method according to Claim 7 wherein
 11 the step of heating includes passing hot air between a
 12 plate or plates positioned a short distance above and
 13 below said rotating surface, or heating said plate or
 14 plates by induction.

15 Claim 9. The method according to Claim 1 wherein
 16 the step of distributing comprises the steps of:

17 heating said coated material in a vessel to
 18 sufficiently high temperature to maintain the coating
 19 material in liquid form;

20 dispersing said individual mass components of core
 21 material into said coating material in said vessel; and

22 stirring the contents of said vessel to form said
 23 suspension of individual mass components distributed
 24 throughout said coating material.

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1 Claim 10. The method according to Claim 1 wherein
 2 the rotating surface is oriented at an acute angle
 3 relative to horizontal.

4 Claim 11. The method according to Claim 1 further
 5 comprising the step of adjusting the thickness of the
 6 coating material on said core material by adjusting the
 7 rotational speed of said surface.

8 Claim 12. The method according to Claim 1 further
 9 comprising the step of adjusting the thickness of the
 10 coating material on said core material by adjusting the
 11 viscosity of the liquid coating.

12 Claim 13. The method according to Claim 1 further
 13 comprising the step of adjusting the thickness of the
 14 coating material on said core material by adjusting the
 15 rate at which said suspension is fed onto said rotating
 16 surface in said step of feeding.

17 Claim 14. The method according to Claim 1 further
 18 comprising the step of adjusting the thickness of the
 19 coating material on said core material by adjusting the
 20 wetted surface of the rotating device.

1 Claim 15. The method according to Claim 1 further
2 comprising the steps of:

3 draining a portion of said coating material, which
4 is fed as part of said suspension to said rotating
5 surface, by providing porosity in said rotating surface
6 as with a mesh cover or porous material or perforated
7 material disposed in the form of a cone or bowl in spaced
8 relation above a further receiving surface;
9 centrifugally dispersing the coated mass
10 components, which are larger than the interstices or
11 perforations of said mesh cover, along said mesh cover
12 while partially draining the liquid coating material, by
13 gravity, such on and/or centrifugal force, away from the
14 coated mass components as the mass components move along
15 the mesh cover; and
16 passing said liquid coating through the mesh cover
17 and recycling the passed liquid coating material.

18 Claim 16. The method according to Claim 1 further
19 comprising the steps of:

20 solidifying said droplets of coating liquid by
21 centrifugally projecting them from said rotating surface
22 through ambient air or gas (heated or unheated, depending
23 on whether the coating is a melt or a solution);
24 collecting the solidified droplets of coating
25 material; and
26 recycling the collected droplets of coating
27 material.

1 Claim 17. The method according to Claim 1 further
2 comprising the steps of:

3 solidifying said droplets of coating material; and
4 recycling the solidified droplets of coating
5 material by returning them to said suspension.

6 Claim 18. The method according to Claim 1 further
7 comprising the step of adding a solvent for said coating
8 material to dissolve the coating material prior to or
9 during the formation of the suspension to permit coating
10 or to reduce the thickness of the coating material on
11 said coated mass components.

12 Claim 19. The method according to Claim 1 wherein
13 said core material is insoluble in said coating material.

14 Claim 20. The method according to Claim 1 wherein
15 said core material is at least partially soluble in said
16 coating material, and wherein the time from initial
17 contact between said core and coating materials to
18 solidifying of said coating material is sufficiently
19 short to prevent significant dissolution of said core
20 material into said coating material.

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1 Claim 21. The method according to Claim 1 wherein
 2 the core material or a component contained thereon reacts
 3 with the coating material or a component contained
 4 therein to form an initial solid wall at the periphery of
 5 each individual mass component before said coating
 6 material solidifies.

7 Claim 22. The method according to Claim 1 wherein
 8 said core material is in the form of liquid droplets
 9 having a higher viscosity than that of the coating
 10 material.

11 Claim 23. The method according to Claim 1 further
 12 comprising the step of hardening the coated mass
 13 components by transferring them to a chemical hardening
 14 bath.

15 Claim 24. The method according to Claim 23
 16 wherein said coating material is a gelatin and said
 17 hardening bath includes glutaraldehyde.

18 Claim 25. The method according to claim 23
 19 wherein the coating is gelatin and hot gas, air or
 20 non-solvent liquid is contacted with the gelatin to cause
 21 cross-linking and insolubilization.

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1 Claim 26. The method according to Claim 22
 2 wherein said individual mass components are generally
 3 spherical particles having diameters in the range of 10
 4 micrometers to 10 millimeters.

5 Claim 27. The method of claim 1 wherein the
 6 coating liquid is a suspension containing fine insoluble
 7 particles which become part of the coating on the core
 8 particles, and are equally as well distributed in the
 9 excess coating liquid.

10 Claim 28. The method according to Claim 1 wherein
 11 said suspension is flung radially outward along said disc
 12 surface in radially-extending angularly-spaced grooves
 13 formed in said surface.

14 Claim 29. In a process for coating particles with
 15 a liquid coating, a method for obtaining individually
 16 coated particles while simultaneously facilitating
 17 removal of the coated particles from excess coating
 18 liquid with which the particles are mixed in a
 19 suspension, the method comprising feeding the suspension
 20 to a rotating surface to separate the suspension into
 21 coated particles and atomized liquid droplets expelled
 22 circumferentially from the surface, and rotating the

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1 surface at a speed for obtaining a predominance of the
 2 excess pure coating droplets of a predetermined size
 3 which is smaller than the size of the coated particles.

4 Claim 30. The invention of Claim 29 wherein the
 5 volume percentage of particles to be coated in the
 6 suspension is in the range 10-35%, preferably 20-35%.

7 Claim 31. The invention of claim 29 wherein
 8 coated particles of temperature-labile material
 9 (chemicals, enzymes, biological cells) are formed with
 10 simultaneous formation of smaller droplets of excess
 11 coating material, so rapidly that little or no
 12 degradation or denaturation occurs.

13 Claim 32. The invention of claim 29 wherein the
 14 core mass components to be coated are poorly wetted by
 15 the coating liquid (wetting angle less than 90°) but are
 16 completely coated by virtue of having been completely
 17 immersed while in suspension and having the process of
 18 liquid spreading and particle radial passage and
 19 solidification occur too rapidly for the uncovering of
 20 the core to occur.

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1 Claim 33. A product comprising (a) individual
 2 mass components of core material having the form of solid
 3 particles, aggregates formed by granulation, or liquid
 4 droplets coated or encapsulated in a liquid core
 5 material, and (b) droplets of pure liquid coating
 6 material of significantly smaller size than the coated
 7 mass components, the product being produced by the
 8 process as claimed in claim 1.

9 Claim 34. Apparatus for coating or encapsulating
 10 individual mass components of core material having the
 11 form of solid particles, aggregates formed by
 12 granulation, or liquid droplets with a coating of
 13 material that is less viscous than the core material and
 14 solid at normal room temperatures but liquid at elevated
 15 coating temperatures, or in the form of a solution during
 16 the coating process, said apparatus comprising container
 17 means for containing the individual mass components of
 18 core material and the liquid coating material in the form
 19 of a suspension, feed means for feeding the suspension
 20 from the container means onto a rotating surface for
 21 centrifugally separating and dispersing the suspension
 22 into (1) droplets of pure coating material and (2)
 23 individual components of said core material coated with
 24 said coating material, cooling means for cooling the
 25 coated individual mass components or for removing solvent

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1 therefrom to solidify the coating material, and means for
 2 controlling the apparatus to produce a predominance of
 3 the droplets of excess liquid coating as droplets of a
 4 predetermined size smaller than the size of the coated
 5 individual mass components.

6 Claim 35. The invention of claim 34 wherein the
 7 controlling means includes means for relating the speed
 8 of rotation of the surface to the predetermined size of
 9 the droplets.

10 Claim 36. The invention of claim 34 including
 11 means for separating the coated individual mass
 12 components from the droplets of pure coating material.

13 Claim 37. The invention of claim 34 including
 14 heating means for heating a region at said rotating
 15 surface for maintaining the coating material in liquid
 16 form at the rotating surface.

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Fig. 1

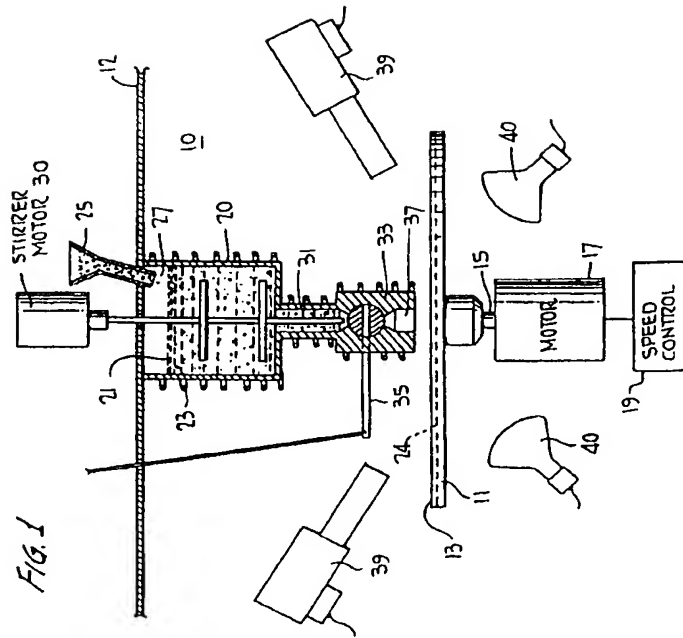


Fig. 2

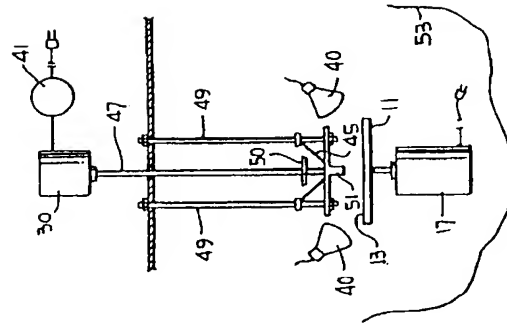
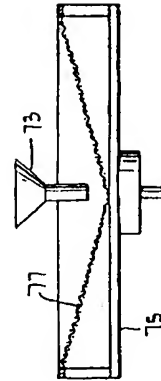


Fig. 5



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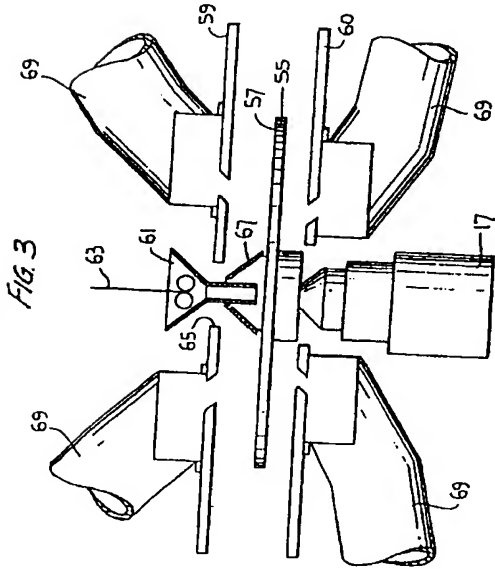
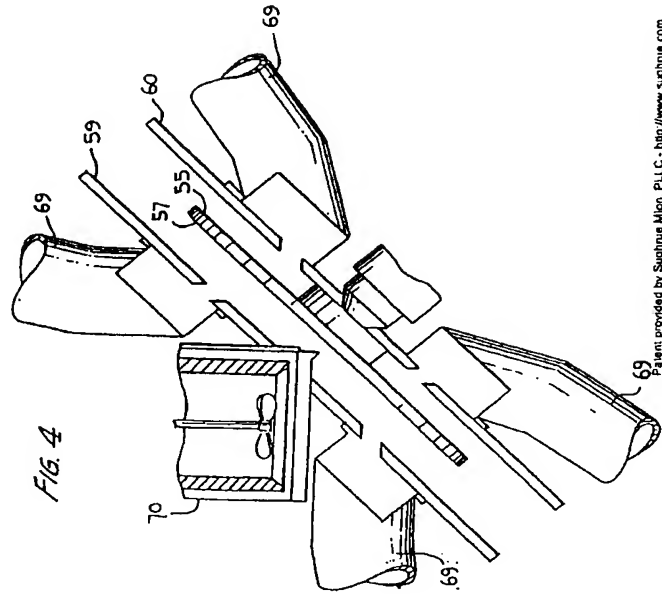


Fig. 4



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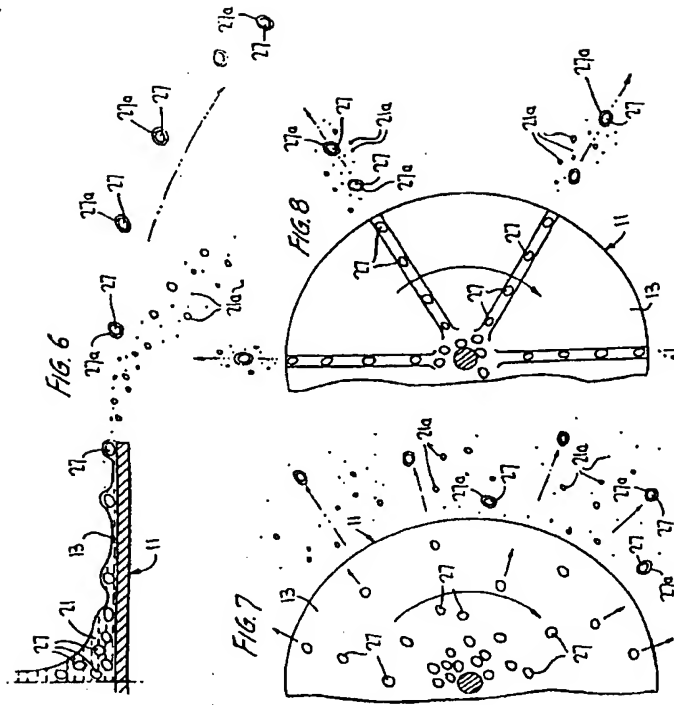


Fig. 9 (PRIOR ART)



Fig. 10 (PRIOR ART)

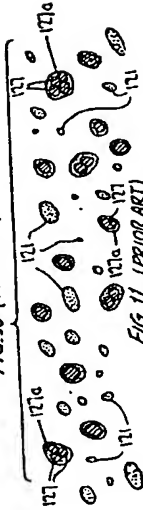


Fig. 11 (PRIOR ART)



INTERNATIONAL SEARCH REPORT

PCT/US 85/00827

1. CLASSIFICATION OF SUBJECT MATTER (If several classifications apply, use each one.)

According to International Patent Classification (IPC) or to both National Classification and IPC

TPC⁴: B 01 J 13/02; A 61 J 3/07

II. FIELDS SEARCHED

Minutem Documentation Searched :

Classification Symbols

A 61 J

— **Abstract** —

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched *

III. DOCUMENTS CONSIDERED TO BE RELEVANT

Allegation	Citation of Document, " with indication, where appropriate, of the relevant passages "	Referent to Claim No. "

Category	Item	Value
A. General Information	1. Name of the organization	ABC Corporation
	2. Address	123 Main Street, New York, NY 10001
	3. Phone number	(212) 555-1234
	4. Fax number	(212) 555-5678
	5. E-mail address	info@abc.com
	6. Website	www.abc.com
	7. Industry	Technology
	8. Type of organization	Public Company
	9. Date of incorporation	January 1, 1990
	10. Fiscal year end	December 31
B. Financial Data	1. Revenue	\$1,234,567
	2. Net income	\$123,456
	3. Operating expenses	\$1,111,111
	4. Capital expenditures	\$50,000
	5. R&D expenses	\$25,000
	6. Depreciation and amortization	\$10,000
	7. Interest expense	\$5,000
	8. Income tax expense	\$10,000
	9. Dividends paid	\$20,000
	10. Earnings per share	\$1.23
C. Management and Governance	1. CEO	John Doe
	2. CFO	Jane Smith
	3. Chairman of the Board	Robert Johnson
	4. Board members	John Doe, Jane Smith, Robert Johnson, Mary White, David Brown, Susan Black, Michael Green, Patricia Red, Christopher Blue, Jennifer Purple
	5. Executive compensation	See separate report
	6. Board composition	50% Independent, 50% Executive
	7. Board diversity	30% Women, 20% Minorities
	8. Board independence	100%
	9. Board tenure	3 years
	10. Board committees	Audit, Compensation, Nominations, Sustainability

tober 1978, see column 3, lines 14-68;
US, A, 4123206 (CLARENCE C. DANNELLY) 31 Oc-
column 4, lines 1-43; figure 1

29, 33, 34, 38

A US, A, 4386895 (LESTER A. SODICKSON) 7 January 1983, see column 3, lines 33-68 (cited in the application)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		Relevant to Claim No.
Category	Citation of Document, with indication, where appropriate, of the relevant passages	
A	DE, B, 1185109 (VITAMINS LTD.) 7 January 1985 see column 7, lines 10-65; figure 2	1,7,9,34
A	FR, A, 1433421 (DUNLOP RUBBER CO.) 21 February 1966 & GB, A, 1090971 see page 1, left-hand column, paragraph 2 page 6, left-hand column, paragraph 3 (cited in the application)	1

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/US 85/00827 (SA 9533)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 17/09/85

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4123206	31/10/78	US-A- 4218409	19/08/80
US-A- 4386895	07/06/83	None	
US-A- 2955956		None	
GB-A- 873757		None	
DE-B- 1185109		None	
FR-A- 1433421		GB-A- 1090971	

For more details about this annex :
see Official Journal of the European Patent Office, No. 12/82